The O-Directed Free Radical Hydrostannation of Propargyloxy Dialkyl Acetylenes with Ph3SnH/cat. Et3B. A Refutal of the Stannylvinyl Cation Mechanism

Personal Account

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The O-Directed Free Radical Hydrostannation of Propargyloxy Dialkyl Acetylenes with Ph_3SnH/cat. Et_3B. A Refutal of the Stannylvinyl Cation Mechanism

Karl J. Hale,* Soraya Manaviazar, and Hamish A. Watson[a]

Dedicated to the memory of Professor Leslie Hough Ph.D, D.Sc, FRSC, of King's College London, who passed away peacefully at his home in London on Sunday August 6, 2017, aged 92 years. Born in Salford, England, he was one of the UK's most distinguished and eminent organic chemists of his generation, making many powerful and useful research contributions to the field of total synthesis and carbohydrate chemistry, including invention of the high intensity, non-caloric, sweetener Sucralose (Splenda®). His work was recognised with numerous honours that included the RSC Haworth Medal and the ACS Claude Hudson Award.

Abstract: In this Personal Account, we will give an overview of the room temperature O-directed free radical hydrostannation reaction of propargylically-oxygenated dialkyl acetylenes with Ph_3SnH and catalytic Et_3B/O_2 in PhMe. We will show how this excellent reaction evolved, and how it has since been used to stereoselectively construct the complex trisubstituted olefin regions of three synthetically challenging natural product targets: (+)-pumiliotoxin B, (−)-(3*R*)-inthomycin C, and (+)-acutiphycin. Throughout this Account, we will pay special attention to highlighting important facets of the I–$SnPh_3$ exchange processes that have so far been used in the various different steric settings that we have addressed, and we will document the range of cross coupling protocols that have critically underpinned the first successful applications of this method in complex natural product total synthesis. Last, but not least, we will comment on various aspects of the O-directed free radical hydrostannation mechanism that have been published by ourselves, and others, and we will discuss all of the factors that can contribute to the observed stereo-and regio-chemical outcomes. We will also challenge and refute the recent non-directed stannylvinyl cation mechanism put forward by Organ, Oderinde and Froese for our reaction, and we will show how it cannot be operating in these exclusively free radical hydrostannations.

Keywords: O-Directed Free Radical Hydrostannation with Ph_3SnH/cat. Et_3B, Propargylically-Oxygenated Alkyl Acetylenes, Stannylvinyl Radical, β-Stannylvinyl cation, Vinylperoxy radical, Trisubstituted Stannylvinyl Radical H-Atom Abstraction, Vinylstannane isomerisation, Allylic 1,3-strain and 1,2-strain, Internal Ligand Enhanced Radicalophilicity, Ph_3Sn radicals have higher electron affinity, The magnitudes of polar solvent rate accelerations observed for genuinely ionic reaction mechanisms

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1. Introduction and Historical Background

The first example of an O-directed free radical hydrostannation of a monoalkyl acetylene can be found in the 1975 report of Corey and Wollenberg in *JOC*,[1] who demonstrated that the propargyl THP-ether **1** underwent a highly stereo- and regio-selective hydrostannation reaction to give the (*Z*)-configured vinylstannane **2**, almost exclusively

(Scheme 1), when heated with neat Bu_3SnH and catalytic AIBN at 80 °C for 2 h.

Although Corey and Wollenberg[1] never went so far as to state that the kinetic (*Z*)-selectivity that they had just observed was probably due to an O-coordinative directing effect from the propargylic ether upon the stannane, later publications from other laboratories subsequently made it clear that significant internal O-coordination of the stannane was probably responsible for the observed stereochemical outcome. This, as well as the much greater degree of hyperconjugative stabilisation for the internally-coordinated (*Z*)-stannyl vinyl radical by the Sn moiety, and the transition state for H-atom abstraction from the stannane being far less hindered for the (Z)-stannylvinyl radical, both strongly favour the formation of **2** as the initial product.

A really key observation made by Corey and Wollenberg was that for high kinetic (Z)-selectivity to be observed, the reaction time had to deliberately be kept short, and the reaction temperature could not be allowed to exceed 80 °C during that period.[1] Indeed, when the direct purification of **2** was attempted by high temperature vacuum distillation at 0.1 mm pressure and 140–142 °C, extensive vinylstannane isomerisation occurred, due to stannyl radical addition-elimination proceeding reversibly upon the initially formed

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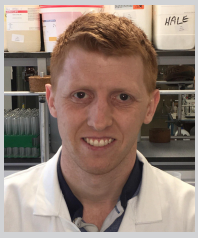
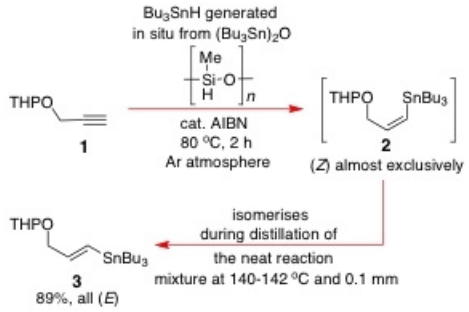


Mr Hamish A. Watson is a native of rural Gloucestershire, England, but he did his undergraduate studies in the School of Chemistry & Chemical Engineering at Queen's University Belfast, graduating with an M.Sci Honours Degree in Chemistry in June 2016, having done undergraduate research work in the group of Professor Paul J. Stevenson in the final year of his degree. In September 2016, he began his studies for the Ph.D degree in Organic Chemistry in the Hale group, where he has been doing research in complex molecule total synthesis, physical organic chemistry, in the development of new synthetic methods and in organotin chemistry.



E. J. Corey and R. H. Wollenberg *J. Org. Chem.* **1975**, *40*, 2265.

Scheme 1. Corey and Wollenberg's seminal discovery of the thermally mediated *O*-directed free radical hydrostannation with ***neat*** Bu_3SnH/cat. AIBN.

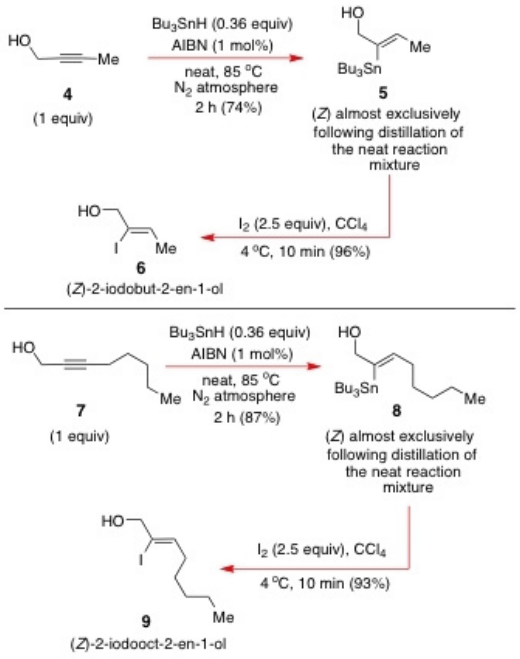
(*Z*)-vinylstannane product, which ultimately led to the thermodynamically more stable (*E*)-vinylstannane **3** being isolated, in preference to **2**, in 89 % yield on 38 g scale.

Following Corey and Wollenberg's seminal report, a further 7 years elapsed before Professor Harry Ensley's team at Tulane University disclosed their study of the O-directed free radical hydrostannation of disubstituted acetylenic alcohols **4** and **7** with *sub-stoichiometric* quantities of neat *n*-Bu_3SnH (0.36 equiv) and catalytic AIBN at 85 °C (Scheme 2).[2] Again, both reactions were found to be highly regio- and stereo-selective, with the α-stannylated (*Z*)-trisubstituted alkenes **5** and **8** being formed exclusively in very high yield. Yet again, Ensley never proposed that the reactions were O-directed, despite this now seeming to be the case.

Notwithstanding only two examples of the O-directed free radical hydrostannation process being reported by Ensley,[2] the excellent regio- and stereo-control observed was striking, to the extent where other teams were soon attracted into the area, curious to see whether the process was general in its scope, or whether higher quantities of Bu_3SnH could effect a full conversion of the starting propargylic alcohols into the product (*Z*)-α-vinylstannanes, to make the process of much greater synthetic utility.

Foremost amongst these early contributors were Taddei and Nativi who, in 1988, reported their detailed study of the scope and reliability of Ensley's *neat*, thermally-mediated, *n*-Bu_3SnH/AIBN hydrostannation method, when applied to other propargylically-oxygenated dialkyl acetylene substrates.[3]

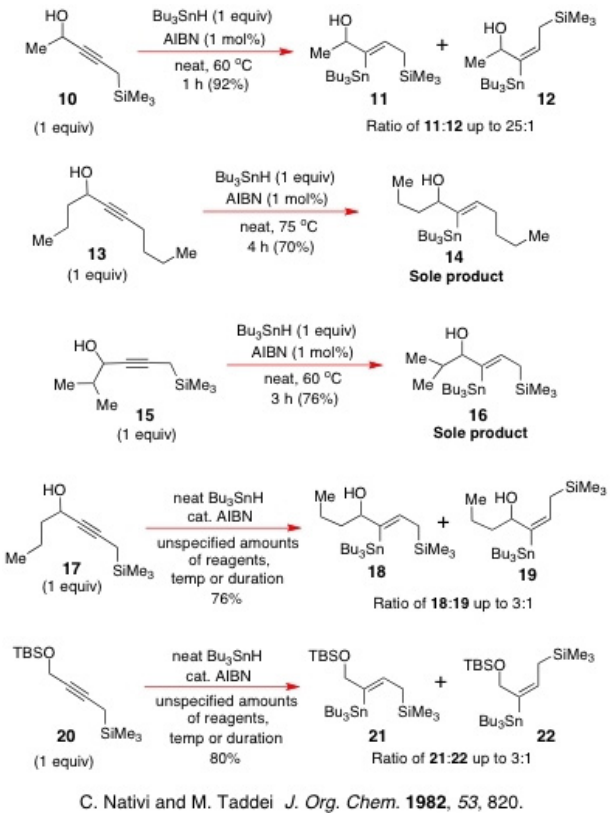
Specifically, their extensive screening of this reaction, under a range of conditions, led them to conclude that the very best hydrostannation outcomes were typically obtained when the reactions were conducted with just 1 equiv. of *neat* Bu_3SnH and 0.01 equiv. of AIBN at 60–75 °C for 1–4 h, whereafter the Ensley products were often isolated in excellent



H. E. Ensley, R. R. Buescher, and K. Lee *J. Org. Chem.* **1982**, *47*, 404.

Scheme 2. Ensley's first application of the thermally mediated *O*-directed free radical hydrostannation of dialkyl propargyl alcohols with *neat* Bu_3SnH and cat. AIBN at 85 °C.[2]

yield with very high levels of (*Z*)-selectivity (see Scheme 3). *It was Taddei and Nativi who first proposed that the propargylic O-atom of such alkyl acetylenes was coordinatively directing the highly regiocontrolled outcome of these α-addition reactions*, although no firm experimental evidence was ever offered by these workers to support their contention despite its high credibility. However, since that time, firm experimental evidence for O-coordinative control has now been conclusively gathered by our team in two propargylically-oxygenated probe systems, using the Ph_3SnH/cat. Et_3B/O_2 variant of the O-directed free radical hydrostannation reaction, and this mechanistic work has unambiguously negated any suggestion that the observed α-regiochemical outcome of these addition reactions is primarily determined by electronic factors inherent in the starting alkyl acetylenes, most especially -I inductive effects from the propargylic O-atom. Indeed, it now appears conclusive that alkyne ground state polarity plays only a minor role in determining the regiochemical outcome of such hydrostannation reactions in propargylically-oxygenated alkyl acetylene systems. We will return to this point later on, in Section 5, when we discuss the likely mechanism of these reactions, and the results obtained with trifluoromethyl acetylenic alcohols, where ground state polarity and O-directive effects *both* determine reaction outcome.



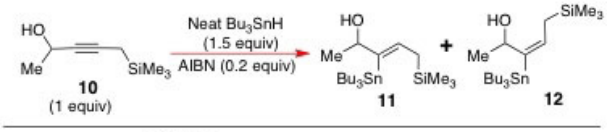
Scheme 3. Some representative optimised examples from Nativi and Taddei's 1988 study of the thermally mediated *O*-directed free radical hydrostannation with ***neat*** Bu_3SnH and cat. AIBN.[3]

It was Taddei and Nativi who *first* suggested that the observed stereochemical outcome of these reactions was likely kinetically controlled. Indeed, they observed that if significant excesses of Bu_3SnH and AIBN were employed alongside prolonged high reaction temperatures, this significantly lowered the observed (*Z*)/(*E*)-selectivity, by promoting a separate reversible tributylstannyl radical addition/elimination reaction upon the initially formed kinetic (*Z*)-vinylstannane products. The latter type of tin radical-mediated isomerisation mechanism had first been proposed as far back as 1967, but it was further invoked by Taddei and Nativi to explain their observations in these systems.

Although the 1988–89 work of Nativi and Taddei[3] did indeed confirm the fundamental essence of Ensley's report on a much larger set of disubstituted alkyl propargyl alcohol substrates (Scheme 3), and it did show that other O-substituents (e.g OMe, OTBS, OAc) could all additionally direct the trialkyltin substituent to the α-position of the starting acetylene, even so, several significant issues did emerge from their more thorough screening and modification of the original Ensley *neat* hydrostannation protocol.

First, despite good product conversions typically being encountered when 1 equivalent of neat Bu_3SnH and 0.1 equiv. of AIBN were used at 60 °C for short periods, as soon as the amount of *n*-Bu_3SnH and AIBN was collectively increased, great stereochemical variations started to result (Table 1). Second, prolonged reaction times and higher reaction temperatures that significantly exceeded 60 °C were often highly detrimental to the final *(Z)/(E)*-selectivity attained. Third, the overall extent of conversion of the starting alkyne into the product vinylstannane could vary quite significantly from run-to-run, with some attempts at driving these reactions to completion often leading to a massive erosion in the observed *(Z)/(E)*-selectivity, due to the occurrence of competing Bu_3Sn radical induced isomerisation.

Table 1. Nativi and Taddei's 1988 study of how high temperature and excess AIBN could influence the outcome of thermally mediated *O*-directed free radical hydrostannation with a slight excess ***neat*** Bu_3SnH.[3]



T °C	Reaction Time	Ratio of 11:12	% Yield	Remaining 10
rt	8 h	0	NR	100%
60 °C	8 h	8:1	NR	10%
80 °C	8 h	2:1	NR	0%
120 °C	0.2 h	5:1	NR	20%
120 °C	1 h	4:1	NR	20%
120 °C	4 h	2:1	NR	0%
120 °C	8 h	2:1	NR	0%
120 °C	36 h	1:1	NR	0%
200 °C	8 h	1:1	NR	5%

NR = Not Reported

C. Nativi and M. Taddei *J. Org. Chem.* **1988**, *53*, 820.

Indeed, in many of the case studies presented in Table 1, a marked variation in both the reaction yield and the stereochemical efficiency was observed over a quite narrow temperature window (60–80 °C), with the reaction divergence being so profound in some cases that most teams could not possibly rely on such a potentially capricious process underpinning a major total synthesis venture.

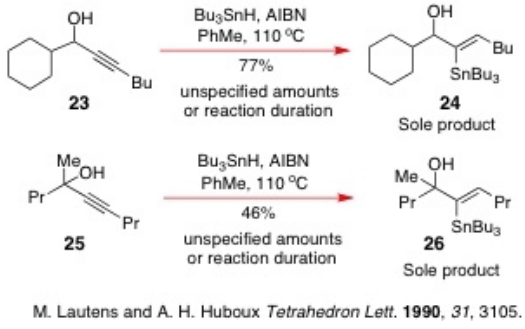
Possibly the large and variable amounts of starting alkynol left behind in some *neat* Bu_3SnH/AIBN hydrostannations might be a manifestation of the often inefficient mixing and inherent inhomogeneity of these processes with some substrates, since clearly there is no solubilising solvent present, other than the Bu_3SnH itself. In addition, the higher reaction temperatures needed to drive some hydrostannations forward might actually be helping to accelerate the free

radical mediated decomposition of the starting Bu_3SnH into $(Bu_3Sn)_2$ and H_2 which could also be leading to reduced product yields.

Another drawback of the Ensley/Taddei *neat* Bu_3SnH/AIBN hydrostannation method lies in its significant incompatibility with thermally-sensitive alkyne samples.

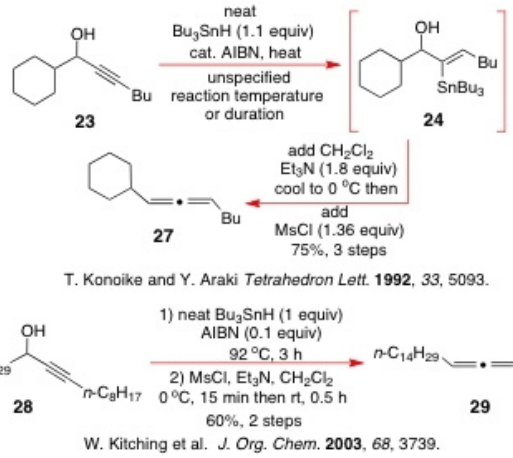
It is also very difficult to perform tandem O-directed alkyne free radical cyclisation reactions via the *neat* thermal free radical hydrostannation procedure which further limits its utility.

While Lautens and Huboux[4] did later report that toluene could be used very successfully as a reaction solvent for *O*-directed dialkyl acetylene free radical hydrostannations with *n*-Bu_3SnH and AIBN, their 1990 *Tetrahedron Letters* paper never actually revealed just how much *n*-Bu_3SnH or AIBN was typically needed to produce a successful outcome, nor did it provide a general substrate concentration at which high stereo- and regio-control was typically observed. Indeed, no representative experimental procedure or guidance was given in this paper, other than the reaction had to be conducted in PhMe at reflux (Scheme 4). Given Corey and Taddei's prior observations that (*Z*)/(*E*)-isomerisation of vinylstannanes can often be problematical at temperatures much above 80 °C, it does seem likely that significant reaction variation might potentially be encountered during attempted applications of the 110 °C method to complex propargylically-oxygenated dialkyl acetylene systems. Nonetheless, this paper did break important new ground in that it dispensed with the neat Bu_3SnH procedure and this did assist greatly in the future development of this field.



Scheme 4. Lautens and Huboux's key report that PhMe could be successfully used as the reaction solvent for *O*-directed free radical hydrostannations of disubstituted alkyl propargyl alcohols with Bu_3SnH/cat AIBN at 110 °C.[4]

Apart from the greatly variable stereocontrol and poor overall conversion issues that can sometimes attend the high temperature Bu_3SnH/cat. AIBN thermal alkyne hydrostannation method, another attendant disadvantage of this method resides in the great sensitivity of many of its vinylstannane products towards protodestannylation on silica gel (or alcohol solvents such as MeOH).[5,6] This is a fact that was specifically highlighted by Trost and Ball[5] in a review on alkyne hydrometallation, and also by Konoike and Araki[7] who specifically commented that: *"These stannylated alcohols were sensitive to silica gel chromatography and used without purification for the second step…"* during their representative application of the O-directed free radical hydrostannation method to alkynol **23** in a new synthesis of chiral allenes via O-mesylation and elimination (Scheme 5).[7,8]

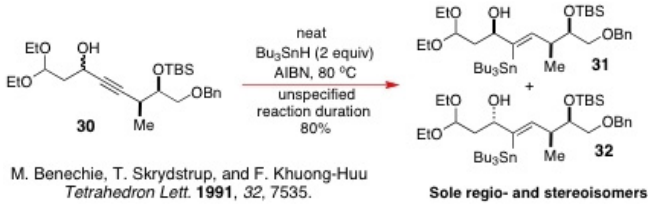


Scheme 5. Konoike and Araki's use of the neat Bu_3SnH/cat. AIBN hydrostannation method for a new allene synthesis. Unfortunately, this paper gave limited experimental details and used the crude vinylstannane products directly to avoid protodestannylation on SiO_2.[7] Subsequently Kitching et al.[8] refined their method and published a detailed experimental protocol for the synthesis of **29** that can now be considered representative.

While for this particular application, the presence of Bu_3SnH or other associated impurities was of little real consequence, this would certainly not be the case if a Stille or other related Pd-mediated cross-coupling was required for subsequent trisubstituted alkene elaboration, where the presence of either excess *n*-Bu_3SnH or other tin impurities could adversely impact the final reaction outcome and yield. Indeed, for the greater majority of such couplings, pure vinylstannane coupling partners are typically essential for success. Thus, this frequent inability to purify the sensitive vinyltributyltin products from the precursor alkynes that often remain at reaction end (or from other tin by-products) is yet another inherent disadvantage and complication of the Bu_3SnH dialkyl-acetylene O-directed hydrostannation method. However, *it is not generally a problem for vinyl triphenylstannanes* which are usually quite stable towards SiO_2 flash chromatographic purification.

Given these various issues, and the difficulty of reaction scale-up, it is perhaps not too surprising to find that Khuong-

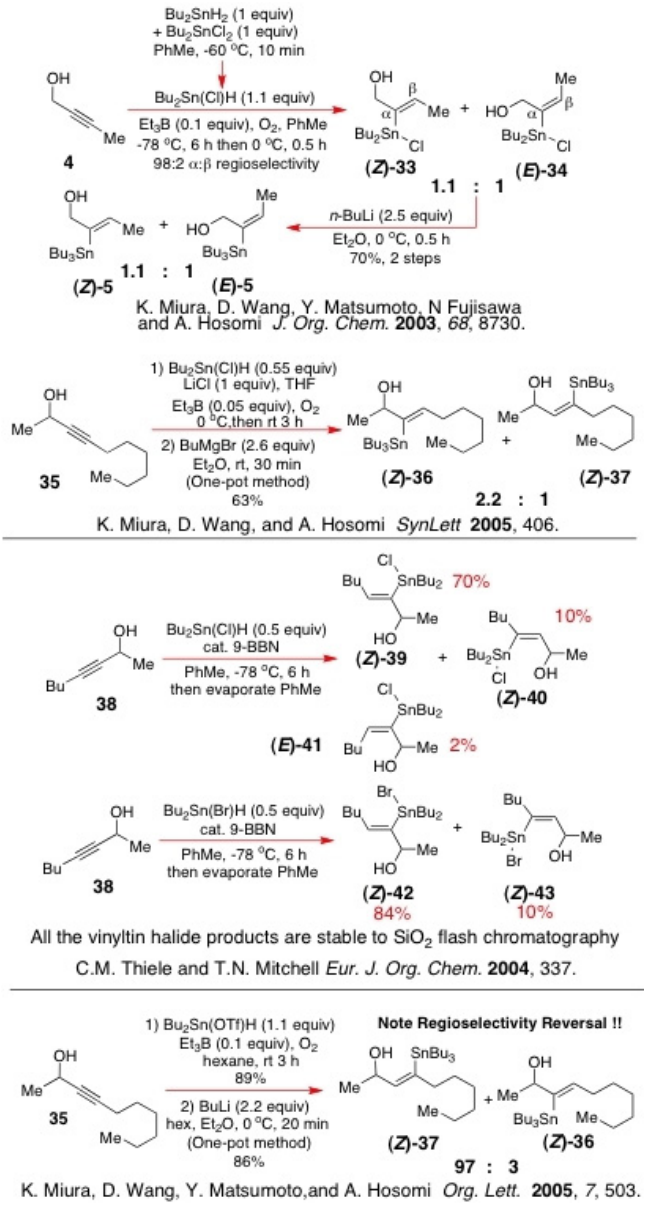
Huu and coworkers never ultimately utilised their *neat* Bu_3SnH/cat. AIBN O-directed free radical hydrostannation reaction on **30** in their eventual total synthesis of (−)-maytansinol despite their initial intent to rely on such a step (Scheme 6).[9]



Scheme 6. Khuong-Huu's use of the neat Bu_3SnH/cat. AIBN hydrostannation method for the synthesis of potential maytansinoid precursor.[9]

Due to the reliability issues and other difficulties that often attend application of the high temperature Bu_3SnH/cat. AIBN hydrostannation method, many groups have sought much milder, more reproducible, and more effective reagent alternatives for implementation of the O-directed free radical hydrostannation on propargylically-oxygenated dialkyl acetylenes, to get a much more dependable (*Z*)-outcome, and some of these efforts are detailed in Scheme 7.[10,11,12] However, even these new protocols do not always perform well, having disadvantages such as poor *E/Z* stereoselectivity, low regiocontrol, difficult reagent preparation, high reagent instability or, in some cases, incompletely documented experimental procedures.

While, in some instances, such as with Miura and Hosomi's remarkably elegant $Bu_2Sn(OTf)H$ reagent[10] (which is used alongside cat. Et_3B/O_2 in hexane at rt), a superb contra- regioselectivity is observed in favour of the β-anti-addition product (Scheme 7), this remarkable success does come at a price, inasmuch as the reagent is quite difficult and tricky to prepare, and it also needs to be generated *in situ* because of its high instability. While the same is true for the analogous halogenotin hydrides of Hosomi/Miura[11] and Mitchell,[12] and their Bu_2SnH_2 precursor, in the case of $Bu_2Sn(OTf)H$, the unique β-regiochemical outcome and high (*E*)/(*Z*)-stereocontrol that it imparts does bring about a great reward for all that effort. However, this is not the case for the $Bu_2Sn(Hal)H$ reagents, except when 9-BBN is used as the free radical initiator[12] and the reactions are conducted at −78 °C, whereupon decent *E/Z*-selectivities often result.



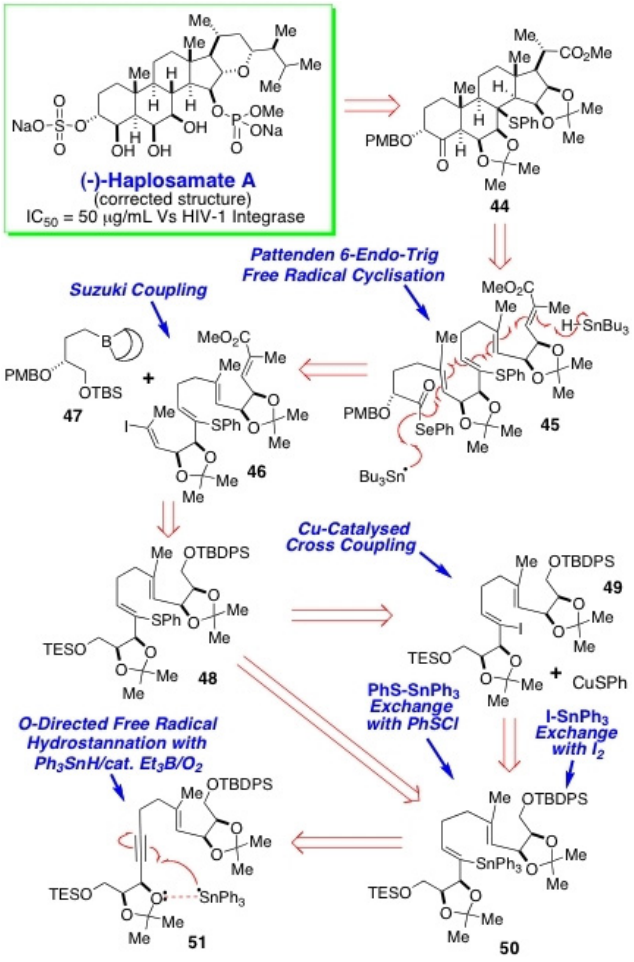
Scheme 7. Miura, Hosomi and Mitchell's $Bu_2Sn(X)H$/cat. R_3B methods for O-directed dialkylacetylene free radical hydrostannation, and Miura-Hosomi's halogen alkylation.[10,11,12]

2. Our Investigations into the Use of Ph_3SnH/cat. Et_3B/O_2 in PhMe for the RT O-Directed Free Radical Hydrostannation of Propargylically-Oxygenated Dialkyl Acetylenes

How we became interested in the O-directed free radical hydrostannation of propargylically-oxygenated dialkyl acetylenes was as a result of our work on the development of a possible synthetic route to (−)-haplosamate A[13] in 2002,

under the auspices of EPSRC grant GR/N20959/01. As part of that effort, we wished to evaluate whether the O-directed free radical hydrostannation of alkyne **51** with Ph_3SnH/cat. Et_3B/O_2 in PhMe at rt (Scheme 8) would *efficiently and reliably* construct the vinylstannane **50** with high stereo- and regio-control. Our ultimate aim was to elaborate **50** into the vinyl sulfide **45** via the vinyl iodide **46**, exploiting a copper-catalysed thiolate cross coupling reaction for the conversion of **49** into **48** or a direct conversion of **50** into **48**. Polyene **45** was the key intermediate that we required for the planned implementation of a Pattenden-type tandem acyl radical cyclisation reaction[14] that we thought might potentially lead to the highly oxygenated steroid system **44**, which could then be further advanced towards (−)-haplosamate A.

At the time when we first conceived this approach, we were only too aware of the highly variable reaction outcomes and yields that could frequently attend applications of the high temperature *n*-Bu_3SnH/AIBN method (Table 1). The



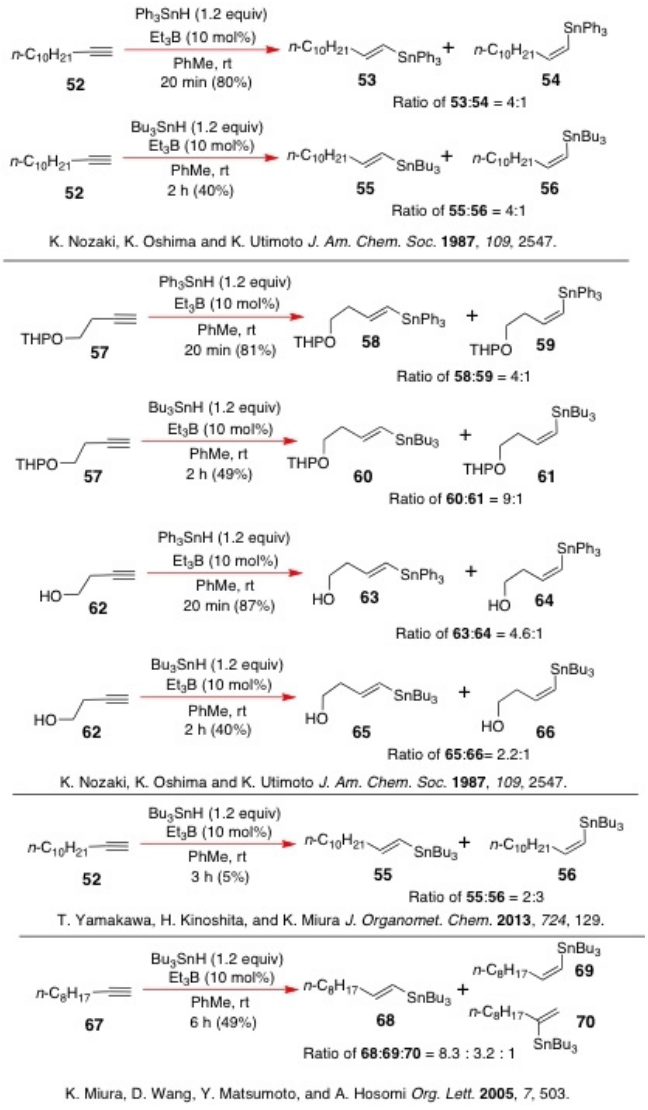
Scheme 8. Our retrosynthetic planning for (-)-haplosamate A.

multiple deficiencies of this prior art thus led to us to explore the possibility of using Ph_3SnH under the catalytic Et_3B/O_2/PhMe rt initiating conditions of Utimoto.[15] We were led in this general direction by the 1987 report of Oshima and Utimoto in *JACS*,[15a] who observed that this reagent system typically gives rise to *far superior* yields and outcomes in alkyne free radical hydrostannation reactions than does Bu_3SnH,[15,16] when used with a catalytic quantity of the initiator Et_3B/O_2 in PhMe under identical circumstances (see Scheme 9 for a comparison); an observation that has since been made by many groups, including our own.

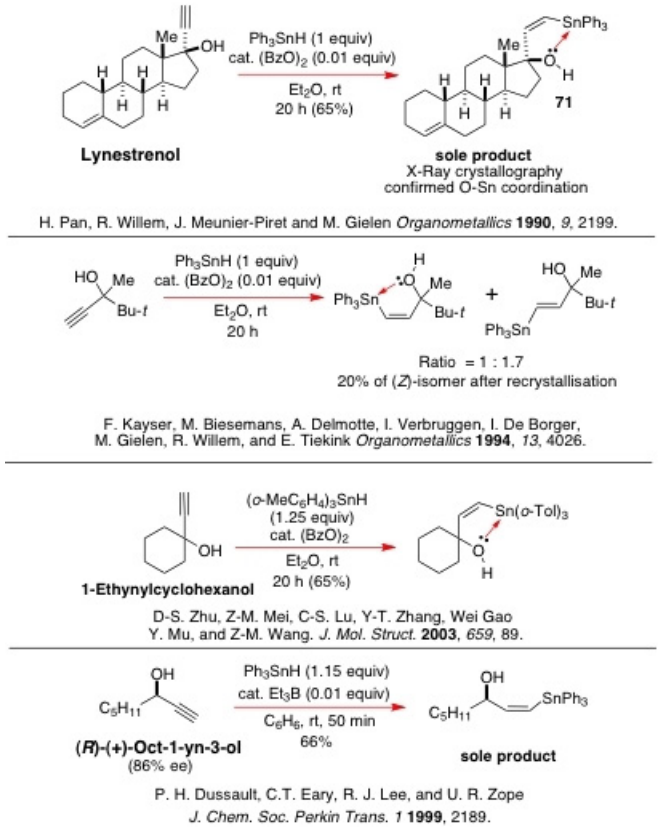
We were also cognizant of the generally good (*Z*)-selective O-directed free radical hydrostannation outcomes that had previously been reported for propargylically-oxygenated terminal acetylenes with triaryltin hydrides and 0.01 equiv. of benzoyl peroxide in Et_2O at rt by the groups of Willem,[17] Gielen,[18] and Mu;[19] and also by Dussault[20] who used Ph_3SnH and 0.01 equiv. of Et_3B/O_2 as the initiator (Scheme 10). Indeed, their contributions to the area of O-directed free radical hydrostannation can only be regarded as outstanding, since their reports are, for the most part, very well documented and, in the case of the former three teams, they additionally provided the first hard physical evidence (X-ray crystallography and NMR) for the existence of a coordinative interaction between the tin grouping and the β-allylic OH in the products, which was strongly suggestive of the propargylic hydroxyl likely directing the observed regio- and stereo-chemical outcomes, which some would consider extraordinary and unusual.

It transpired that the O-directed free radical hydrostannation of propargylically-oxygenated disubstituted alkyl acetylenes had not been systematically studied in any detail with Ph_3SnH/cat. Et_3B/O_2 in PhMe at rt, and it was only after we became deeply immersed in our own independent work in this area that we eventually came across the lone report of Willem and Gielen in 1994,[21] where they revealed that the alkynol **72** (Scheme 11) underwent a highly regio- and stereo-selective O-directed free radical hydrostannation in 67 % yield when it was submitted to the rt Ph_3SnH, 0.01 equiv. of Et_3B/O_2/PhMe procedure for 20 h. Despite this excellent result, which some might attribute to a favourable Thorpe-Ingold type O–Sn coordinative effect, no other examples of the process were ever reported by the Willem/Gielen team following this disclosure. Nor did they manage to successfully manipulate the vinyl triphenylstannane **73** into any representative target trisubstituted alkene that possessed three C–C bond branches. Essentially this novel hydrostannation reaction lay ignored.

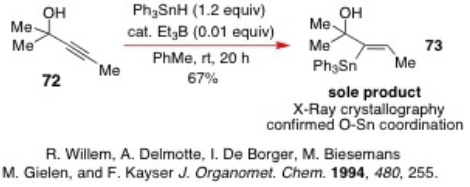
Given this situation, and the fact that Malacria and coworkers had later reported[22] that the synthetic conversion of vinyl triphenylstannanes into target trisubstituted alkenes could potentially be problematical, *it was not at all clear*



Scheme 9. The lower reactivity of Bu_3SnH vs Ph_3SnH in alkyne hydrostannations under rt cat. Et_3B/O_2/PhMe initiated conditions.[15,16,10]



Scheme 10. The O-directed free radical hydrostannation of various terminal acetylenes with different Ar_3SnH reagents in Et_2O and C_6H_6 under a variety of rt initiated conditions.[17,18,19,20]



Scheme 11. The very first example of an O-directed free radical hydrostannation reaction being conducted on a propargylically-oxygenated dialkyl acetylene with Ph_3SnH and a catalytic quantity Et_3B/O_2 in PhMe under rt conditions.[21] We emphasise here that Et_3B does *not* serve as a catalyst in these reactions, since it is always consumed and destroyed by the O_2. Rather, throughout this article, the terminology "cat. Et_3B" simply refers to the Et_3B being used in catalytic quantity.

whether allylically-oxygenated trisubstituted vinyl triphenylstannanes would ever be synthetically manipulable substrates, even if the rt Ph_3SnH/ cat. Et_3B/O_2/PhMe hydrostannation procedure was ultimately found to be of excellent and widespread utility. We will return to this point again later when we discuss the I–Sn exchange reactions of trisubstituted vinyl triphenylstannanes, and the synthetic manipulation of the so-derived vinyl iodide products (Section 3).

All told, therefore, when we first entered this area in 2002, it was of considerable interest to us to thoroughly examine whether the Utimoto/Oshima Ph_3SnH/0.1 equiv. of Et_3B/O_2 rt hydrostannation procedure in PhMe would indeed give rise to superior results when it was applied to a diverse collection of propargylically-oxygenated dialkyl acetylenes. We also wished to establish whether it would be possible to elaborate the product vinyl triphenylstannanes into all-carbon trisubstituted olefin structures of significant complexity, should a generality of scope be demonstrated in the O-directed alkyne hydrostannation itself.

We will now discuss some of the theoretical concepts and initial mechanistic thinking that underpinned our decision to investigate whether Ph_3SnH/cat. Et_3B/O_2 in PhMe at room temperature might give improved O-directed hydrostannation outcomes.[23]

First and foremost in our minds[23] was our belief that the three electron-withdrawing Ph groups on Ph_3SnH would likely enhance coordination of the tin atom to the propargyloxy substituent very substantially. We considered that such an O-coordination event would likely lengthen and further weaken the already weak Sn–H bond in Ph_3SnH, to favour and promote a subsequent H-atom abstraction from the Sn atom that would then produce a hypervalent O-coordinated triphenylstannyl radical that would likely have enhanced longevity in solution, when compared with an uncoordinated $Ph_3Sn^{\cdot}$ or a corresponding O-coordinated-tri-*n*-butylstannyl radical. We considered that the lifetime of the O-complexed radical would probably be extended for two reasons. First, it would be generated at rt; and, second, the central tin atom in an O-coordinated Ph_3Sn radical system would probably experience greatly magnified steric crowding. We hypothesised that the extended lifetime of an O-coordinated Ph_3Sn radical might markedly favour its internal addition to the α-position of a dialkyl acetylene, in a manner analogous to, but more efficiently than, that observed by Taddei and Nativi.[3]

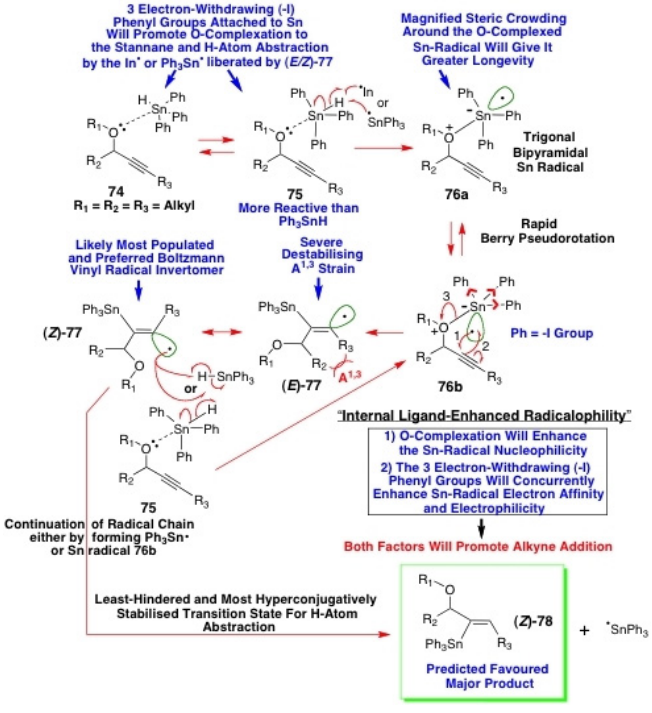
Additionally, the significantly enhanced electrophilic radical character of a hypervalent O-coordinated Ph_3Sn radical **76**, alongside its concurrently increased nucleophilicity (arising from donation of the O-lone pair), could reasonably be expected to promote a rapid room temperature radical addition to an electron-donating dialkyl acetylene; much moreso than the corresponding addition involving an analogous O-coordinated Bu_3Sn radical, due to the latter primarily being a nucleophilic radical with a greatly reduced electron affinity, with the consequence that it would have a greatly attenuated ability to accept a donated electron from a partnering donor alkyne.

In this regard, unlike its hypervalent O-coordinated Ph_3Sn radical counterpart **76**, which would have three electron-withdrawing −I Ph groups attached to the central tin, an O-coordinated Bu_3Sn radical would instead have three inductively electron-donating +I *n*-butyl groups attached to the tin atom. We deemed that this simple change in the electronics around the Sn atom would be so profound that it would alter both the character and overall pattern of reactivity of the O-coordinated Ph_3Sn radical towards a partnering nucleophilic alkyne, to make the Sn radical much more readily receive a donated electron from the alkyne and so undergo a far more favourable and productive union.

Thus, it was our *a priori* contention that these combined effects would create a unique and hitherto undocumented electronic situation around the central tin atom, where considerably enhanced electrophilic and nucleophilic radical character would both be simultaneously imparted to the internally O-complexed hypervalent Ph_3Sn radical, rather like a Captodative Effect.

We now term this new concept in radical chemistry "**Internal Ligand-Enhanced Radicalophility**" and we define it as "the phenomenon where internal heteroatom electron pair-coordination to a metal radical with multiple −I groups, gives rise to a new type of hypervalent/hypercoordinate radical that has greatly enhanced nucleophilic and electrophilic properties and increased overall reactivity". We will revisit this concept again later on when we discuss key aspects of the O-directed free radical hydrostannation mechanism with dialkyl acetylenes.

However, for now, if we consider the likely situation that would arise after an O-coordinated Ph_3Sn radical **76b** has just added to a tethered alkyne (Scheme 12). We reasoned that the rapidly inverting pair of bent alkyl α-triphenylstannylvinyl radicals (***E***)-**77** and (***Z***)-**77** so generated would preferentially H-atom abstract from the Ph_3SnH or its O-coordinated Ph_3SnH counterpart (intermediate **75**) *very rapidly* when the vinyl radical **77** was in the (*Z*)-config-



Scheme 12. The theoretical concepts and initial mechanistic thinking[23] that underpinned our selection of Ph_3SnH/cat. Et_3B/O_2 for the rt O-directed free radical hydrostannation of propargylically-oxygenated dialkyl acetylenes, and our proposed new concept of **"Internal Ligand-Enhanced Radicalophilicity"**.

uration, due to the (*Z*)-transition state minimising $A^{1,3}$ strain between the olefinic carbon side chains, unlike its (*E*)-α-triphenylstannylvinyl radical invertomer **(*E*)-77**, which would encounter maximal $A^{1,3}$ strain. So although we recognised that the (*E*)- and (*Z*)-dialkyl α-triphenylstannylvinyl radicals might be rapidly interconverting, to us, it seemed far more likely that the (*Z*)-isomer **(*Z*)-77** would preferentially H-atom abstract from a bulky stannane donor, *since a (Z)-transition state would be of much lower energy*, and it would encounter far less steric repulsions. The latter process would, of course, liberate either a new Ph_3Sn radical, or a complexed Sn radical **76b**, both of which would propagate the forward radical chain reaction. A Ph_3Sn radical could eventually do this by generating **76a** and **76b** from the more reactive **75**, which would create a further pool of Ph_3SnH for additional complexation and reaction via the more favourable O-directed hydrostannation mode.

In other words, in full accord with the predictions of the Curtin-Hammett principle, the initial *Z/E*-selectivity would not be governed by the relative proportions of the two vinyl radical invertomers that would be generated in solution, but by the difference in energy of the two respective types of transition state for H-atom abstraction by **77** from the Ph_3SnH or **75**. Given the greater degree of branching and larger effective size of a Ph_3Sn group compared with a Bu_3Sn, we thus anticipated that improved selectivity might result in the H-atom abstraction step from the use of bulkier Ph_3SnH but naturally, of course, we could not guarantee this *a priori.*

A further insight into our overall strategic planning can now be given. While, at first sight, many organic chemists might consider that a very bulky Ph_3Sn-group would encounter a far more destabilising $A^{1,3}$ strain between the attached Ph groups and the adjoining β-alkyl side chain in a (*Z*)-stannylvinyl radical such as **(*Z*)-77** (much moreso than for its (*E*)-geometric counterpart **(*E*)- 77**), it is now a well established fact in organotin chemistry that sterically bulky R_3Sn groups actually have quite a low "effective" repulsive size[24,25] when they are positioned within a C–C-bonded skeletal framework, due to the fact that a C–Sn bond is quite long (*ca.* 2.1-2.2 Å).[25] In essence, the longer C–Sn bond serves to push a physically bulky R_3Sn group quite a large distance away from the carbon backbone to which the group is connected (Figure 1).

In other words, in this situation, it would be the long C–Sn bond that would position the physically large Ph_3Sn group a good distance away from the adjacent freely rotating adjacent *cis*-configured alkyl substituent on the alkene to help nullify the $A^{1,3}$ strain situation.

By way of contrast, if an analogous carbon functional group such as a Ph_3C was attached to the corresponding α-alkenic carbon via a much shorter C–C bond (1.54 Å), it would bring the accompanying Ph substituents into a much

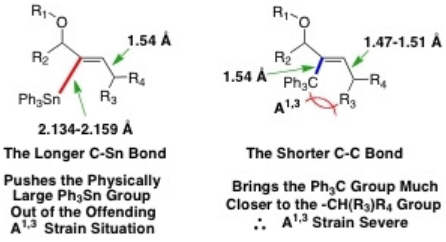


Figure 1. An exaggerated view of how a physically larger Ph_3Sn-group behaves as though it were smaller than a Ph_3C-group in an $A^{1,3}$-strain setting.

closer 1,3-relationship with the olefinic β-alkyl substituent than would be the case with the analogous Ph_3Sn group. The corresponding, C-bonded, Ph_3C group would thus encounter a significantly increased, destabilising, $A^{1,3}$-steric repulsive interaction when compared with a Ph_3Sn group.

The greater length of a C–Sn bond means that when most commonly encountered R_3Sn units are positioned within a C–C-skeletal network, they generally behave as smaller substituents than a Me, in terms of their "effective" intramolecular repulsive size, despite the significantly larger actual physical size of a R_3Sn group (see Figure 1). This is now a fairly well established principle in organometallic chemistry that has been documented on numerous occasions by Davis,[24] Corey,[25] Curran,[26] Kitching[27] and others. In order to emphasize this point, we list here the A values for some common groups: $Ph_3C = 4.9$ kcal mol^{-1}; Me = 1.7 kcal mol^{-1}; $Ph_3Sn = 1.4$–1.5 kcal mol^{-1};[27] i–$Pr_3Sn = 1.1$ kcal mol^{-1}; $Me_3Sn = 1.0$ kcal mol^{-1}.

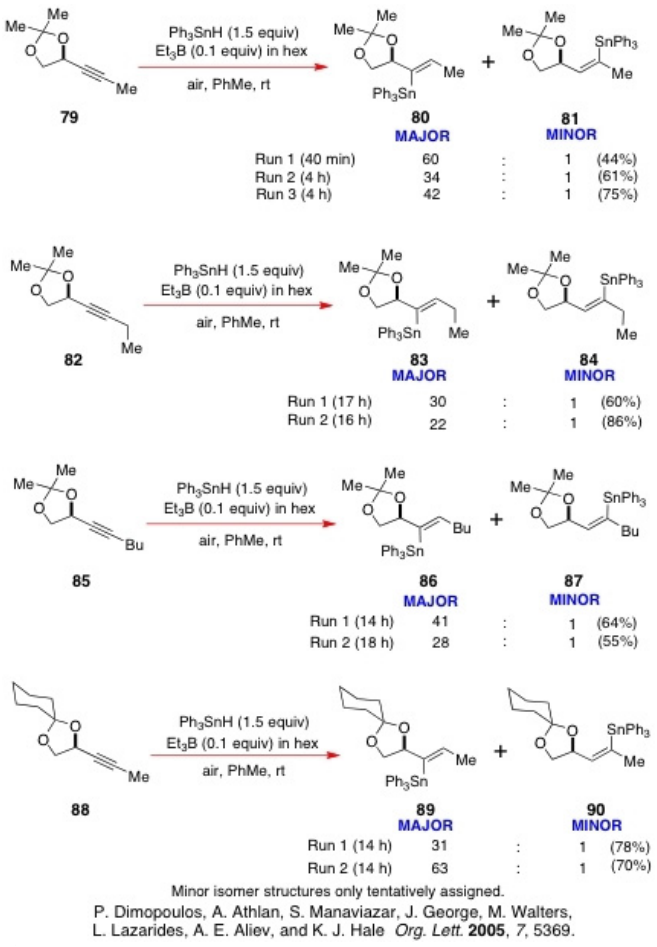
So, all told, we considered that this combination of factors, plus a likely enhanced rate of H-atom abstraction by an intermediary triphenylstannylvinyl radical from Ph_3SnH (or an O-coordinated Ph_3SnH), when compared with Bu_3SnH, would collectively help promote a (*Z*)-selective α-addition of the Ph_3Sn radical to the tethered acetylene with much greater efficiency, and at a faster overall rate. In this regard, it is already widely documented that Ph_3SnH is a superior H-donor than Bu_3SnH in H-atom transfer reactions to most radicals, and so it would be unreasonable to expect this situation not to prevail here when dealing with a highly reactive triphenylstannylvinyl radical.

However, *most importantly*, one particular advantage of generating an O-coordinated hypervalent Ph_3Sn radical at room temperature would probably come from the improved ability to preserve the hypervalent Sn radical for a longer period of time in solution, which we believed would be essential for engaging a typical "nucleophilic" propargylically-oxygenated dialkyl acetylene.

Naturally, higher reaction temperatures would be expected to be much more likely to promote decomplexation of an initially O-coordinated stannyl radical due to the increased

molecular motions and steric repulsions that would accompany such an external energy transfer. So, by operating at a much lower temperature, we felt that we might significantly improve the overall prospects for reliably obtaining improved conversions, stereoselectivities and overall O-directed α-outcomes, although we were aware that Taddei and Nativi had still obtained good α-regiocontrol at 60–80 °C but with somewhat variable stereoselectivity.[3]

Obviously, before we could even contemplate applying this "new" O-directed hydrostannation process in a complex system of the type required to reach haplosamate A, we felt it essential that we establish the viability of the reaction in a series of model systems. Accordingly, we studied the reaction of alkyne **79** with 1.5 equiv. of Ph_3SnH and 0.1 equiv. of Et_3B in PhMe at rt, in the presence of O_2 (Scheme 13). Initially the reaction was run for 40 min, whereupon the desired vinyl triphenylstannane **80** was formed as the major component of a 60 : 1 mixture of **80** and **81** which, after SiO_2 flash chromatographic purification, was isolated in 44% yield. A repeat of this rt stannation twice more, but now for 4 h, improved the yield significantly (75%), and again led to **80** predominating over **81**, but with a reduced level of α:β selectivity (34–42 : 1). Extending the alkyl chain, as in alkynes **82** and **85**, likewise gave good results when the reactions were allowed to stir at rt for 14–18 h. We next examined whether a spiro-ring-fused cyclohexylidene 1,3-dioxolane O-acetal could serve as an effective tin-directing group and, accordingly, acetylene **88** was selected as the substrate for our study. It reacted with Ph_3SnH under our previous reaction conditions over 14 h to give the vinyl triphenylstannane **89** as the major product of a 31–63 : 1 mixture of regioisomers produced with near total stereoselectivity. The yield of hydrostannation was 70–78% and the reaction was extremely clean.



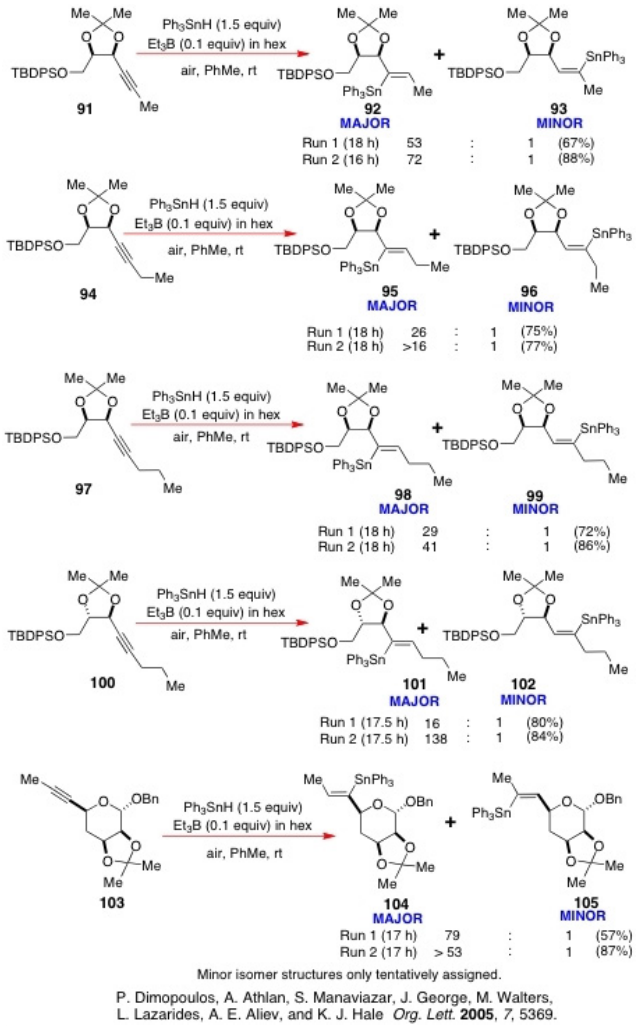
Scheme 13. Our initial investigations into whether disubstituted alkynes with propargyl O-acetals could engage in O-directed free radical hydrostannation reactions with Ph_3SnH/cat. Et_3B/O_2 in PhMe at rt.[23]

Given this outcome, we subsequently decided to probe whether 1,2-disubstituted propargyl 1,3-dioxolane systems with a 1,2-*cis*- or *trans*-disposition of the substituents on the dioxolane ring could undergo O-directed free radical hydrostannation with Ph_3SnH and a catalytic quantity of Et_3B/O_2 in PhMe at rt, and alkynes **91**, **94**, **97** and **100** were accordingly submitted to our standard conditions. In every case, exceptionally good regio- and stereo-control was observed even when higher alkyl groups sat on the β-acetylenic carbon to the propargyloxy group (Scheme 14).

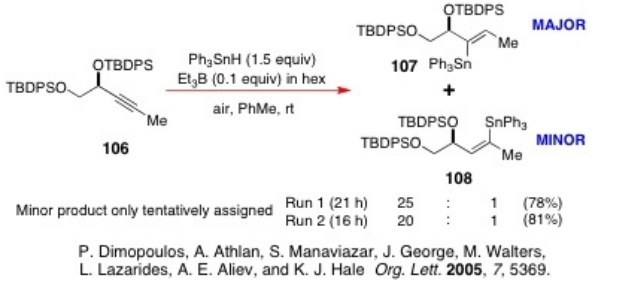
Since a number of pyranoid natural products exist such as (+)-acutiphycin, where a trisubstituted olefin sits adjacent to a pyran ring O-atom, we naturally became interested in determining whether a pyranosidic ring O-atom could engage in a rt O-directed alkyne free radical hydrostannation with Ph_3SnH/cat. Et_3B/O_2 in PhMe and, accordingly, alkyne **103** was investigated as a test case. As can be seen from Scheme 14, alkyne **103** performed admirably in this process, affording **104** as the favoured reaction product with high stereo- and regio-control.

Next we probed whether a disubstituted alkyl-acetylene with a bulky TBDPS group on the propargylic O-atom could successfully O-coordinate with the bulky Ph_3SnH reagent to bring about a rt O-directed free radical hydrostannation under the cat. Et_3B/O_2 conditions in PhMe (Scheme 15). Accordingly, alkyne **106** was evaluated; it provided **107** as the major component of a 20–25 : 1 mixture of vinylstannanes in 78–81% yield, showing that an O-silyl substituent could serve as an efficient O-director group for Ph_3SnH in some situations, analogously to Taddei and Nativi.[3a]

Another question that arose was whether a propargylic OBn group would be able to satisfactorily direct the course of an alkyne hydrostannation with Ph_3SnH/cat. Et_3B/O_2 without the intermediary α-triphenylstannylvinyl radical engaging in a highly deleterious 1,5-H-atom abstraction event at the benzylic position. The latter could potentially cleave the tethered OBn protecting group via a fragmentation to the



Scheme 14. An evaluation of how 1,2-disubstituted dioxolane acetals behave as α-directors in O-directed free radical hydrostannation with Ph_3SnH/cat. Et_3B/O_2 in PhMe at rt.[23]



Scheme 15. Even bulky OTBDPS groups can *occasionally* serve as efficient O-directing groups in unhindered dialkyl acetylene hydrostannations with Ph_3SnH/cat. Et_3B/O_2 in PhMe.[23]

allylic radical, which would be accompanied by a loss of benzaldehyde (Scheme 16). The allylic radical would then go on to abstract hydrogen from the Ph_3SnH. We felt that by laying down a successful marker here we would significantly enhance the future utility of our new hydrostannation method. Accordingly, we examined the hydrostannation of the O-benzylated alkyl acetylene **109** and, to our delight, it proceeded successfully and without any hitch, furnishing the desired vinylstannane **110** as the major product of a 44–59 : 1 mixture of regioisomers **110** and **111** (Scheme 17) in decent yield.

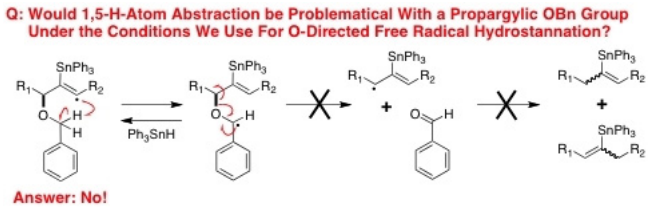
By way of contrast, when Doutheau[28] attempted the free radical cyclisation of iodide **112** under conditions where the Ph_3SnH concentration was deliberately kept low (to prevent quenching of the initially formed primary radical), the subsequently generated vinyl radical immediately engaged in a highly favourable 1,5-H-abstraction event that cleaved the allylic OBn group to ultimately give the deoxygenated products **114** and **115** in high yield (Scheme 18) alongside a small quantity of **113**.

Clearly, by having a significant excess of the Ph_3SnH (1.5 equiv) present throughout the O-directed hydrostannation of **109**, this prevented any such an adverse OBn cleavage event from occurring, leading to an outcome wherein only **110** and **111** were observed.

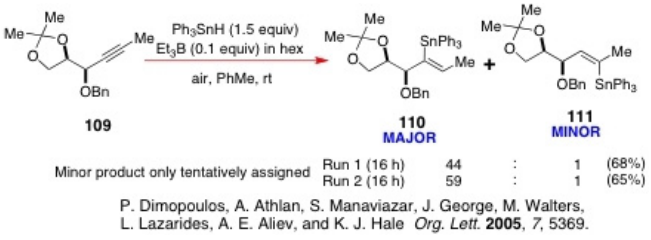
Having established that propargylic O-acetals, O-silyl ethers, and O-benzyl ethers could all serve as efficient Ph_3SnH directors in these alkyl acetylene free radical hydrostannations, we next evaluated a series of propargylic alcohols. Initially, we decided to examine primary alkyl propargyl alcohol substrates and found that these generally performed well either with or without branching in the parent propargylic alcohol (Scheme 19).

With but-2-yn-1-ol (**4**), the O-directed hydrostannation reaction with Ph_3SnH/cat. Et_3B/O_2 in PhMe proceeds with very high (Z)-selectivity and in excellent yield with minimal erosive (*Z*)/(*E*)-isomerisation (Scheme 20).[29] However, we draw specific attention to the fact we did occasionally encounter some isomerisation on some of our early runs, where the (*E*)-isomer **126** was also formed. We now attribute this outcome to photochemical *(Z)/(E)*-isomerisation of the initially formed (Z)-vinylstannane **125** when the reactions were unwittingly exposed to strong natural sunlight for prolonged periods, in the laboratory, in the presence of a slight excess of stannane. However, we have since found that if one works inside a fume cupboard, in normal artificial light, then one can always effect this O-directed hydrostannation reaction with Ph_3SnH/cat. Et_3B/O_2 in PhMe with very high, if not total, (Z)-selectivity *without isomerisation.*

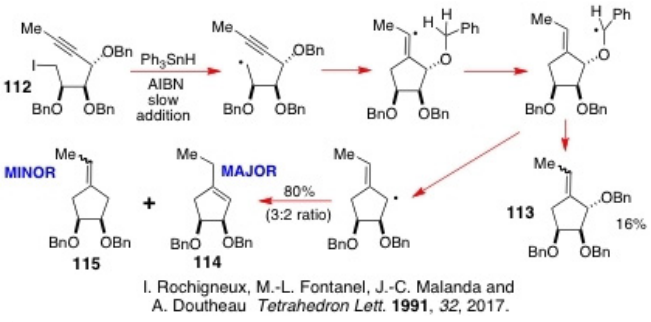
We next examined the viability of the O-directed hydrostannation with Ph_3SnH/cat. Et_3B/O_2 in PhMe on chiral



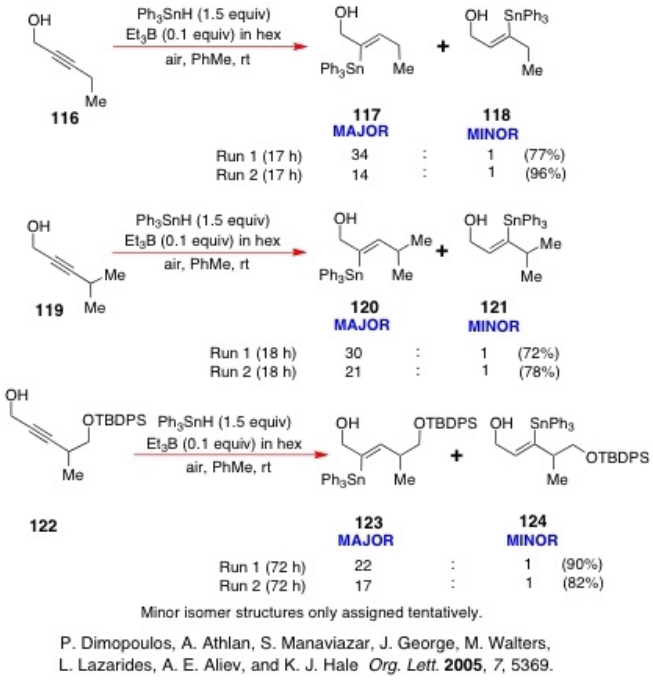
Scheme 16. The potential propargylic OBn fragmentive deoxygenation problem.[28] It is not usually a problem, however, as Scheme 17 shows.[23]



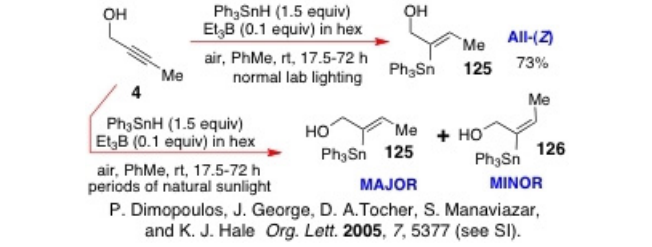
Scheme 17. Propargylic OBn ethers typically work well under our general O-directed dialkyl acetylene free radical hydrostannation conditions; OBn deoxygenation is not usually a problem.[23]



Scheme 18. Deoxygenative 1,5-H-atom abstraction by vinyl radicals that have an allylic OBn when those radicals are generated at very low Ph_3SnH concentration.



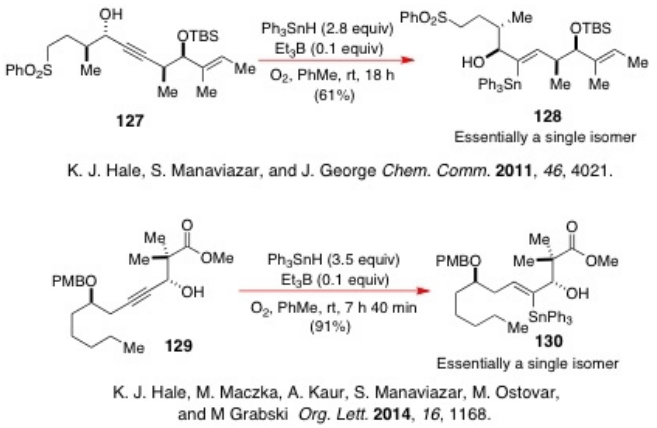
Scheme 19. Primary alkyl propargyl alcohols are viable substrates for (*Z*)-selective O-directed hydrostannation with Ph_3SnH/cat. Et_3B/O_2 in PhMe when the alkyl group has branching.[23]



Scheme 20. An excellent substrate for O-directed hydrostannation with Ph_3SnH/cat. Et_3B/O_2 in PhMe, provided one protects the reaction mixture from exposures to direct, high intensity, natural sunlight! We now have good evidence to show that the latter can cause an excess of Ph_3Sn radicals to be produced in solution by photoinitiation; these can then go on to cause variable (*E*)/(*Z*)-outcomes by reversible addition-elimination of the Ph_3Sn radicals to **125**, if due precautions are not taken. *Indeed, our advice is to protect all O-directed free radical hydrostannation reactions from inadvertent exposure to strong natural sunlight, when they are being conducted.* Normal levels of artificial room lighting generally do not cause such photoinitiated isomerisation events in our experience.[29]

secondary alcohol alkyne substrates, and two representative examples of outcome are shown below in Scheme 21.[30,31]

Yet again, we have observed that secondary dialkyl propargyl alcohols, even complex ones, are viable substrates for these reactions, generally performing well even when the terminal alkyl group on the β-acetylenic carbon is unbranched, and just a simple methyl substituent. Likewise, when the alkyl component of such alcohols contains a γ-alkene, as in **127**, still, 5-*exo-trig* ring closure does not occur to any significant extent at *higher* stannane concentrations (we will revisit this issue later when we discuss the mechanism of the alkyl acetylene O-directed free radical hydrostannation). Moreover, when there is substantial branching at the carbon α- to the propargyl alcohol unit and β- to that alkyne carbon, as in **129**, free radical hydrostannation still proceeds smoothly and with high efficiency (91%). This last reaction is of special note since alkyne **129** also possesses an OPMB group β- to one of the alkyne carbons, and it survives the hydrostannation event unscathed, without undergoing destructive triphenylstannylvinyl radical induced 1,5-H-atom abstraction and subsequent deoxygenative fragmentation or

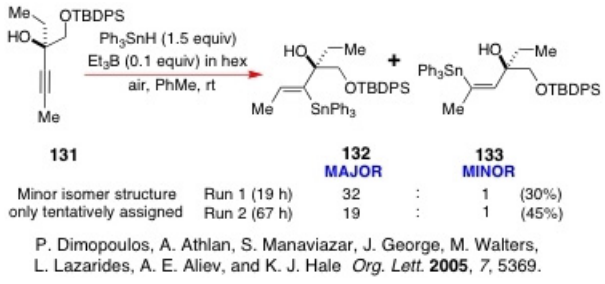


Scheme 21. Some secondary dialkyl propargyl alcohols that have undergone rt O-directed hydrostannation with Ph_3SnH/cat. Et_3B/O_2 in PhMe.[30,31]

cyclisation. Yet again, working at higher stannane concentrations is always advisable when trying to preserve such delicate protecting groups.

Complex branched tertiary alcohols are another set of substrates that will participate in this reaction (Scheme 22) but, in this capacity, they generally always give rise to much poorer overall conversions than other substrate classes; this is especially true when there is significant branching adjacent to the tertiary –OH. Despite this, such reactions nevertheless often proceed very cleanly and with excellent levels of stereocontrol. Tertiary ethers may sometimes undergo the process, but as with tertiary alcohol substrates, it is often difficult to drive these reactions all of the way through to completion, with no reaction being observed at all in some cases. We thus do not recommend tertiary ethers as substrates for future total synthesis efforts that are going to be underpinned by this reaction.

We next examined whether propargylically-oxygenated aryl acetylenes could serve as viable substrates for the O-directed free radical hydrostannation with Ph_3SnH/cat. Et_3B/O_2 in PhMe, and although we did observe good stereocontrol



Scheme 22. Tertiary dialkyl propargyl alcohols in the rt *O*-directed hydrostannation with Ph_3SnH/cat. Et_3B/O_2 in PhMe.[23]

after 16–18 h in the case of phenyl acetylenes **134** and **137** (Scheme 23), we have noted that related α-oxygenated aryl acetylenes can sometimes require much longer reaction times (sometimes of the order of 3 days) and the addition of a significant excess of the Ph_3SnH (an additional 1.5 equiv, plus an additional 0.1 equiv. of the Et_3B, on top of the normal 1.5 equiv. Ph_3SnH and 0.1 equiv. of Et_3B we normally use) in order to obtain the optimal (*Z/E*)-stereoselectivities and conversions. In our view, α-oxygenated aryl acetylenes give much less dependable stereochemical results in the O-directed hydrostannation than do alkyl acetylenes which do, by far, give much more reliable outcomes.

Although, we have indeed obtained some very good results with propargylically-oxygenated aryl-acetylene substrates when R = Ph, with α-regiocontrol always being total, we do not consider aryl acetylenes to be generally high-fidelity substrates for the O-directed free radical hydrostannation process with Ph_3SnH/cat. Et_3B/O_2.

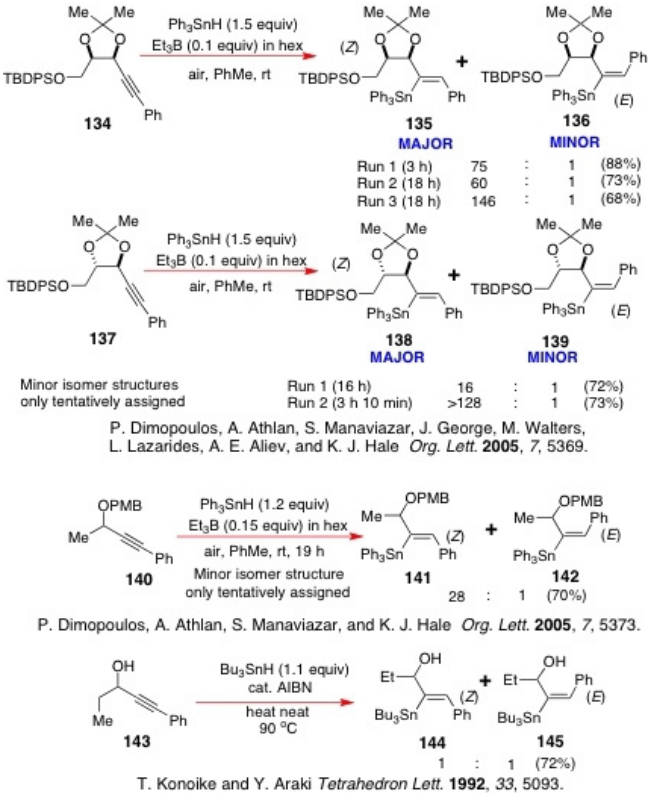
Now despite our 2005 reports on the above three O-directed free radical hydrostannations of the aryl propargyloxy derivatives **134**, **137** and **140** (Scheme 23),[23,32] and the even earlier report of the thermally mediated neat free radical hydrostannation of alcohol **143** by Konoike and Araki in 1992 (Scheme 23),[7] and the subsequent 1999 report of Alami and coworkers,[33] and the example provided by Podesta[34] (see Scheme 24), Organ and coworkers made the claim[35a] that they were the first and only workers to have reported the O-directed free radical hydrostannation of propargylically-oxygenated aryl acetylenes when they published their detailed paper on this topic in 2014, stating that:

"Surprisingly, we could not find any prior reports of radical-mediated hydrostannylation of aryl propargylic alcohols (or their derivatives) in the literature…".[35a]

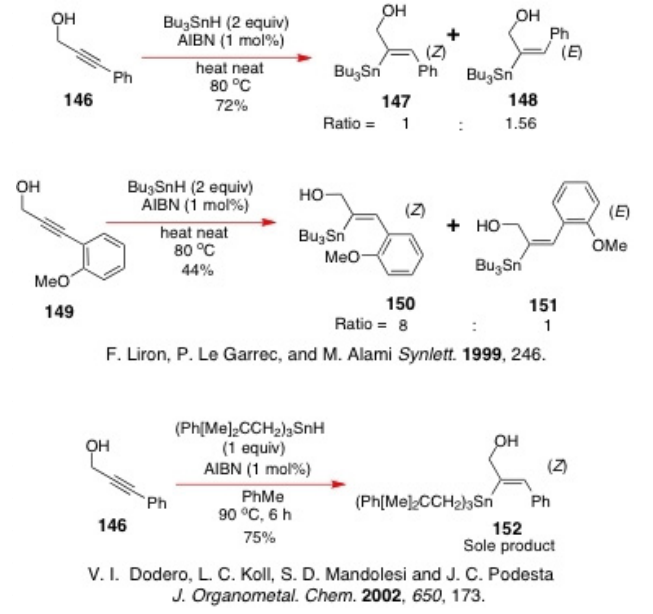
Clearly, the examples that we have provided in Schemes 23[23,32,7] and 24[33,34] show otherwise.

Notwithstanding this lack of due recognition of the prior aryl acetylene O-directed free radical hydrostannation work by this team,[35a] and for the sake of historical completeness of our own present article, we will now present several examples of the Organ group's aryl acetylene free radical hydrostannation outcomes in Scheme 25.[35a] It will be noted that these results[35a] were actually gathered *using our prior Ph_3SnH/cat. Et_3B/O_2 method*,[23] and essentially they confirm and duplicate many of our own independent findings in this area: that such substrates are typically lower fidelity participants in the O-directed free radical hydrostannation process (Scheme 25).

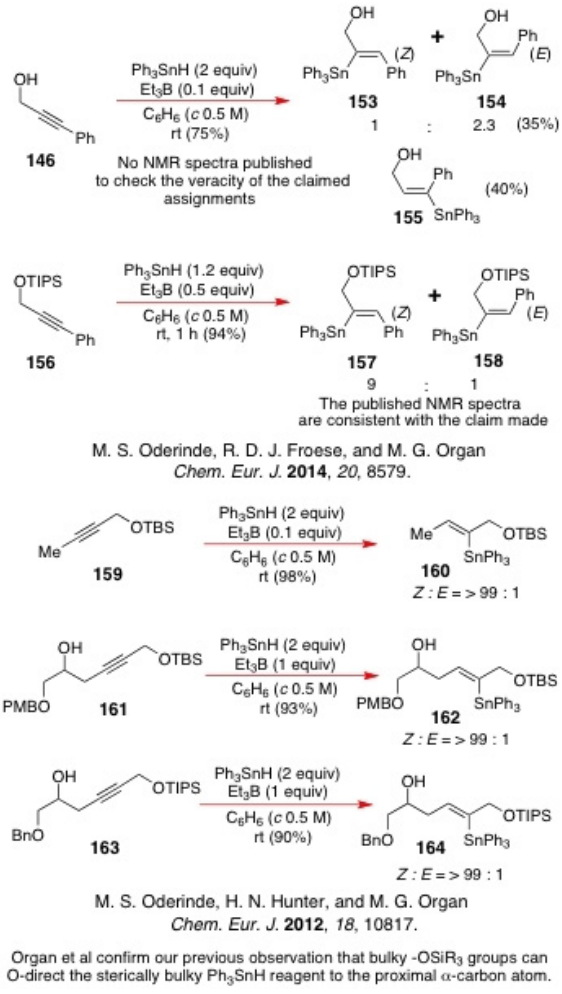
We also list some of the Organ team's other results[36,37] on our far superior hydrostannation of alkyl acetylenes with Ph_3SnH/cat. Et_3B/O_2 in benzene in Scheme 25.[36] The latter work again essentially duplicates and modestly augments our own very extensive work[23,32] on the O-directed hydro-



Scheme 23. The *O*-directed hydrostannation of α-oxygenated phenyl acetylenes with Ph_3SnH/cat. Et_3B/O_2 in PhMe at rt,[23,32] and a comparison with Konoike and Araki's application of the neat thermal Bu_3SnH/AIBN method.[7]



Scheme 24. The *O*-directed free radical hydrostannation of aryl acetylenes conducted by Alami and Podesta over the period 1992–2002.[33,34]



Scheme 25. Some of Organ's *O*-directed free radical hydrostannation reactions on propargyloxy aryl and dialkyl acetylenes conducted using our prior Ph_3SnH/cat. Et_3B/O_2 method[23] in C_6H_6 at rt.[35a,36] Note the high yields, excellent regiocontrol, and superb *Z:E* selectivity that is observed for the alkyl acetylene substrates using our protocol.

stannation reaction of alkyl acetylenes, in which we had already documented its compatibility with homo-propargyloxy functionality and OBn/OPMB ethers in various alkyne substrates, in addition to showing the powerful O-directing effect of propargyl $OSiR_3$ groups on Ph_3SnH alkyne hydrostannation outcomes,[35] as readers will no doubt discern.

Significantly, in all of the rt Ph_3SnH/cat. Et_3B/O_2 alkyl acetylene hydrostannations that the Organ team report using our method (Scheme 25), *they actually observe very high levels of regio- and (Z/E)-stereo-selectivity alongside good yields of product*, as one would naturally expect given the typically excellent performance, high fidelity, and remarkable efficiency of our reaction and method (*vide infra*).

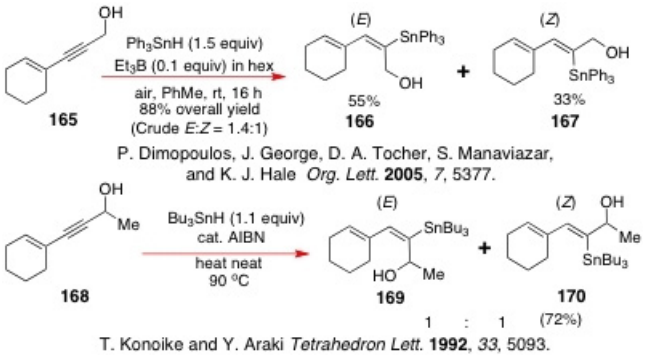
So, for this team to subsequently make the following inaccurate claim[38] about our protocol, when they themselves

had such great success using it,[36] is really quite hard to understand. Nonetheless, this is how they chose to portray our excellent Ph_3SnH/cat. Et_3B/O_2 O-directed free radical hydrostannation method in their 2013 *Chem. Eur. J* report.[38,39] Specifically, it was inaccurately stated: *"However, poor reproducibility with regard to regioselectivity and yield, coupled with difficulty in product isolation relative to nBu_3Sn derivatives, makes the use of Ph_3SnH impractical and less attractive"*.[38] Even more surprising is the fact that this statement was made despite these workers themselves having secured product yields of 90–98% and *Z*-selectivity of the order of 99:1 in all three examples reported in Scheme 25,[36] and us reporting numerous excellent hydrostannation outcomes where the regiocontrol and stereocontrol were always very good and the unoptimised yields were typically high![23,31] We consciously draw attention to this inaccurate portrayal of our method, since it has no absolute basis in fact.[39]

Moreover, as for this alleged "difficulty" that has been suggested to arise during the attempted isolation and purification of trisubstituted vinyl triphenylstannane products,[38] again we must totally controvert this particular claim, since we ourselves have never generally encountered any difficulties during the isolation and purification of any of our trisubstituted vinyl triphenylstannane products. Moreover, such compounds are typically far more stable and easier to purify by SiO_2 flash chromatography than are their vinyl tri-*n*-butyltin counterparts, which can undergo significant, if not total, proto-destannylation when exposed to silica gel, as noted by Konoike and others.[7,5] In fact, it is this added stability of trisubstituted vinyl triphenylstannanes on silica gel that is one of their great attributes and significant advantages for multistep total synthesis.

Moving on from this inaccurate depiction of our work,[38,39] we will now discuss yet another class of disubstituted propargyloxy alkyne substrate that can give rise to quite variable and often quite poor levels of *Z/E* stereocontrol in the O-directed free radical hydrostannation, and these are enynols such as **165** and **168**. Indeed, when we applied our standard rt Ph_3SnH/cat. Et_3B conditions to **165** (Scheme 26),[29] we went on to observe that a chromatographically separable 1.4:1 (*E*)/(*Z*)-mixture of vinylstannanes had formed after 16 h, in which the unanticipated (*E*)-isomer **166** had very marginally predominated over its (*Z*)-counterpart **167**, despite the α-regiocontrol being total, and the overall yield of the hydrostannation process being high!

Undoubtedly, this particular outcome is due to Ph_3Sn radical mediated dienylstannane isomerisation occurring under the room temperature catalytic Et_3B/O_2 initiated conditions. Similar (Z)/(*E*)-stereocontrol problems were also encountered when Konoike and Araki[7] examined the high temperature free radical hydrostannation of the related enynol



Scheme 26. Enynol substrates typically give rise to poor (*Z/E*)-stereocontrol in *O*-directed free radical hydrostannations due to facile isomerisation even at rt in the case of Ph_3SnH/cat. Et_3B/O_2.

168 with neat Bu_3SnH/cat. AIBN at elevated temperature, where similarly a 1:1 mixture was obtained of **169** and **170**.

So, to conclude, we recommend that our rt Ph_3SnH/cat. Et_3B/O_2 reaction protocol is conducted in PhMe with appropriately tailored α-oxygenated dialkyl acetylene substrates, since this type of alkyne typically gives rise to the very best and most reliable outcomes in such hydrostannations. Because of the variable *Z/E* stereoselectivity that is sometimes observed in the free radical hydrostannations of propargylically-oxygenated aryl-acetylenes and enynol derivatives, we ourselves have focused all of our synthetic attention on the much more reliable α-oxygenated dialkyl acetylene class, since these usually react with superb regio- and stereo-control, and in good yield, and this is the domain where the deployment of this powerful new stereoselective reaction will undoutedly have its greatest impact.

3. Reaction Utility. How to Transform α-Triphenylstannyl-Alkenes into Representative Target Alkenes Via I–Sn Exchange and Pd(0) Mediated Cross Coupling

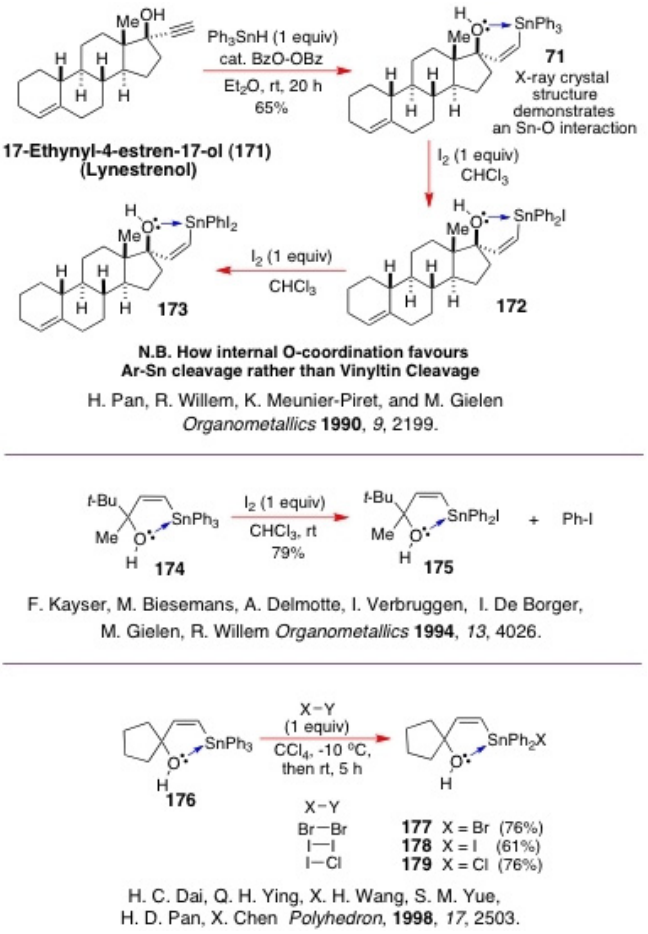
One of the major challenges that had to be confronted in order to turn our newly developed general dialkyl acetylene hydrostannation process, with Ph_3SnH/cat. Et_3B/O_2, from a mere chemical curiosity into a genuinely useful new synthetic method, lay in our successful conversion of the new vinyl triphenyltin products into fully alkylated target trisubstituted alkenes via cross coupling. In this regard, when we first began our work in this area in 2003, the general historical record for achieving this transformation did not look good at all. In particular, a successful direct *regioselective* Stille cross coupling of the vinyl component of a trisubstituted vinyl triphenyltin had never been reported.

The main problem with this particular transformation arises from the phenyl and vinyl groups on tin both having a similar propensity to transmetallate and donate to an aryl-, vinyl- or alkyl-palladium (II) halide intermediate in Stille cross coupling reactions, and statistically there being three phenyl groups capable of being competitively delivered to the Pd relative to only one vinyl group. Thus, the prospects for implementing such a direct coupling process on a complex substrate of great value looked distinctly poor, to say the least, and our own early attempts at doing this soon encountered significant difficulties, with very low yields of product typically being obtained whenever a reaction was observed.

Given this situation, and our great desire to ultimately convert the various α-triphenylstannylated alkene products into a range of representative target trisubstituted alkenes, we decided to investigate ways of successfully converting them into the corresponding vinyl iodides. Although this would now add an extra step onto the overall synthetic process for alkene elaboration, the primary advantage of following this approach would emanate from the much greater range of cross coupling methods that could subsequently be used for alkene construction, and the ability to use an excess of the partnering organometallic donor, particularly with a less precious coupling partner.

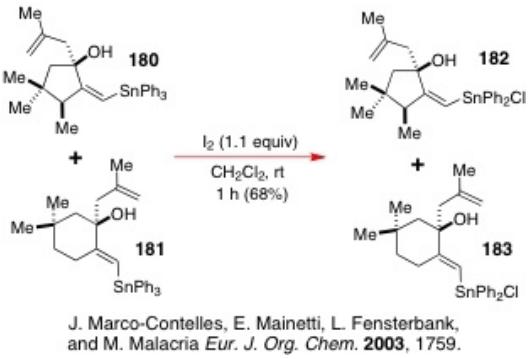
Furthermore, the synthetic elaboration of the product vinylstannanes directly, confines one simply to just using the Stille reaction and, if that Stille process fails, which often it does with complex vinylstannane donors, then there really would be no effective mild alternative for successful alkene elaboration. For all of these reasons, an I–Sn exchange strategy was deemed to be of far greater strategic value for the future deployment of this chemistry in highly complex synthetic situations.

However, at the very outset of our work, even the iodine-tin exchange step did not look as though it would be straightforward, based upon the prior literature reports of such reactions. In this regard, a rather limited number of reports existed on attempted I–Sn exchanges with vinyl triphenylstannanes, and these had almost entirely focused on systems where a tertiary allylic hydroxy was coordinatively interacting with the tin, to preferentially activate the Ph groups towards cleavage, and concurrently hinder electrophilic attack by the I^+ source on the alkene. Thus, when we began our work, no paper had yet been published that had provided a single clear-cut example of the successful conversion of a vinyl-$SnPh_3$ into a vinyl iodide. Instead, one or more of the phenyl groups was always selectively cleaved from the Ph_3Sn moiety in such systems and a vinyl(aryl)tin halide was always typically formed instead (Scheme 27).[17,18,19] Likewise, in other sterically hindered vinyl triphenyltin substrates where the allylic-OH was not internally coordinating, yet again, Ph–Sn cleavage occurred in preference to vinyl-Sn cleavage, and once more vinyl iodide products were not formed (Scheme 28).[22]

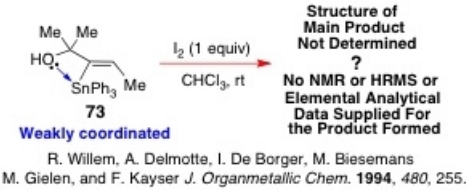


Scheme 27. A summary of the early I–$SnPh_3$ exchange studies that had been carried out on tertiary (*Z*)-β-triphenylstannyl allylic alcohols where a direct Sn–O interaction had been observed.[17,18,19]

However, some glimmer of hope did come from the successful iododemetallation claim of Willem and Gielen on (*Z*)-2-methyl-3-triphenylstannyl-3-penten-2-ol (**73**) in 1994[21] (Scheme 29). In their report, these workers indicated that the triphenyltin residue of **73** could successfully be cleaved with just 1 equivalent of I_2 in $CHCl_3$ at rt. However, a close examination of the experimental section of that paper soon revealed that they had not provided any firm experimental evidence to back up their claim. Specifically, no structure had been formally assigned to the primary product of this reaction, nor had any ^1H or ^{13}C NMR spectral data been provided for the claimed product, to enable others to check the veracity of their assertion. Additionally, HRMS data and an elemental analysis were both missing for the claimed product.



Scheme 28. Malacria's observations on attempted I–Sn exchange in sterically hindered vinyl triphenylstannane systems. Presumably, the Cl in products **182** and **183** comes from traces of HCl in the CH_2Cl_2 solvent or from the work-up.[22]



Scheme 29. Willem and Gielen's claim that I_2 cleaves the Ph_3Sn group from **73**.

Since Willem and Gielen had also highlighted that a weak intramolecular HO–Sn interaction had been detected in the X-ray crystal structure of **73**,[21] this made us somewhat apprehensive about the possible outcome of the aforementioned I–Sn exchange process, most especially given all of the Ar–Sn cleavage problems that had previously been reported by them in internally O–Sn coordinated systems (see Scheme 27). To us, it was far from proven that a vinyl iodide had ever actually been prepared by Willem and Gielen in this reaction, and as well as this, the issue of vinyl iodide stereochemistry still lay unaddressed.

Given our misgivings, and the central importance of this I–Sn exchange process to the eventual outcome of our work, we felt obliged to study the I–Sn cleavage process in considerable detail on a range of trisubstituted vinyl triphenylstannanes prepared through the O-directed hydrostannation reaction,[32] to establish whether trisubstituted vinyl iodides do indeed emerge from such exchange reactions, or vinyltin halides, or both. We were also keen to prove, beyond any doubt at all, that allylically oxygenated vinyl iodides could be readily converted into a range of representative complex trisubstituted olefin target structures via the numerous different Pd(0)-mediated cross coupling protocols that now exist. This would demonstrate unambiguously the great utility of our new trisubstituted olefin synthesis.

It transpires that the retentive I–Sn cleavage of *non-hindered* trisubstituted vinyl triphenyltin systems can be conveniently achieved using either a slight excess of I_2 (1.2 equiv) or *N*-iodosuccinimide (NIS) (1.4 equiv) in CH_2Cl_2 with the former usually being preferred.[32] The reaction is generally conducted initially at low temperature, and then at rt, and typically works very well, it being of wide substrate scope.

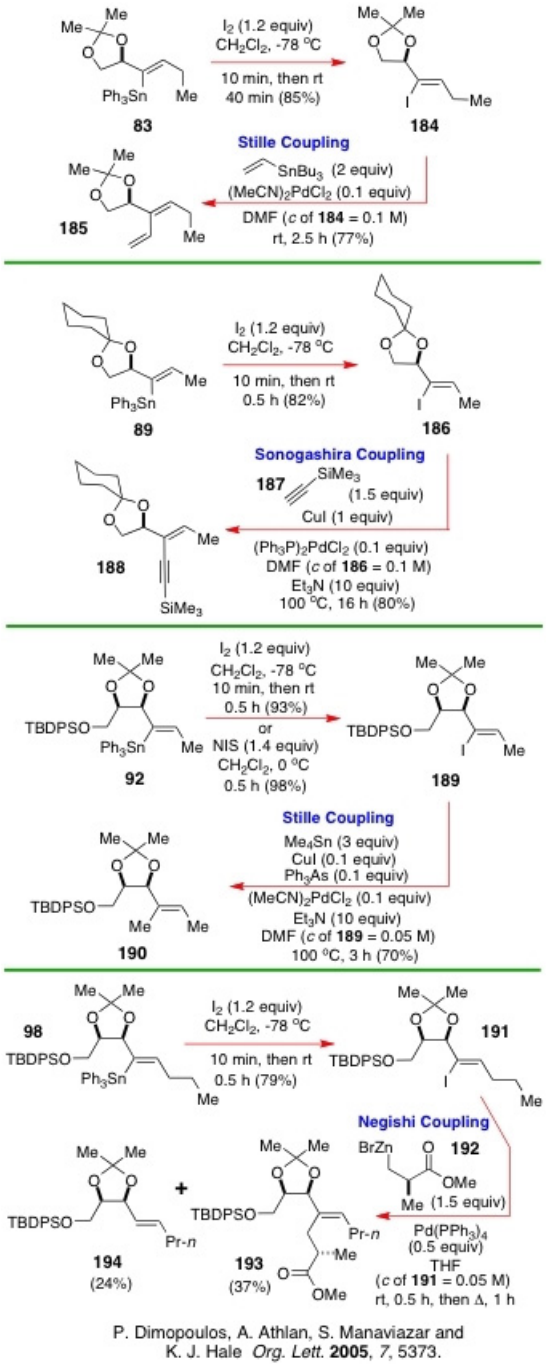
Some of our results are presented in Schemes 30 and 31.[32,30] However, for *more sterically hindered* trisubstituted vinyl triphenylstannanes, often a much greater excess of the electrophilic iodinating reagent is required, *along with a much longer reaction time and*, *in such recalcitrant systems*, *NIS is most definitely a requirement.* We will discuss the issue of I–Sn exchange in hindered vinyl triphenylstannane systems in far more detail when we review our work on (−)-(3*R*)-inthomycin C and (+)-acutiphycin, which has collectively provided many profound and powerful insights into how to accomplish the I–Sn exchange process successfully in hindered, acid-sensitive, vinyl-$SnPh_3$ systems. In the case of (+)-acutiphycin, these successes were achieved through the support of our group by Leverhulme Trust Grant RPG-2015-438.

For now, however, we will confine our discussion to the average, not so hindered, vinyl triphenytin systems that one *typically* encounters, where it is the vinylic component that selectively reacts with I_2 or NIS, as opposed to the phenyl group. Significantly, we have established that these I–Sn exchange processes proceed as normal with total retention of configuration.

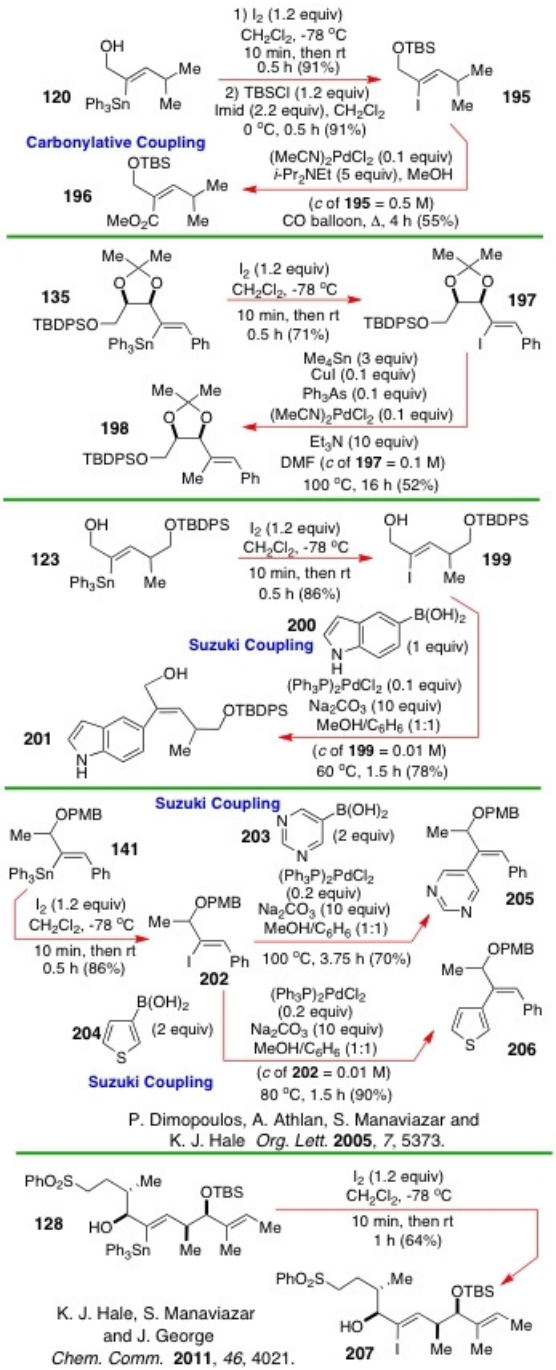
First, we addressed the iododestannylation of **83** with 1.2 equivalents of I_2 in CH_2Cl_2 (Scheme 30).[32] Initially this reaction was commenced at −78 °C for 10 min, and completed by warming to rt for 40 min, whereupon a smooth and total transition occurred into the desired vinyl iodide; **184** was isolated in 85 % yield after SiO_2 chromatography, and it was subsequently converted into the stereodefined diene **185** in 77 % yield by application of a rt Stille process with vinyl tributyltin over 2.5 h (Scheme 30).[32] The entire two step conversion was totally stereoselective and delivered the target alkene with complete preservation of the original vinyl triphenylstannane geometry.

The more sterically hindered O-cyclohexylidenated vinylstannane **89** also successfully underwent I–Sn exchange under near identical conditions (Scheme 30).[32] Again a similar 82 % yield of **186** was obtained, and it too readily participated in a Cu(I)/Pd(0)-promoted Sonagashira cross coupling with TMS-acetylene (**187**) in DMF over 16 h at 100 °C. Once more, both reactions provided an illustrative and stereoselective route to enynes.

Our standard I–Sn exchange conditions also worked well in bringing about the iododemetallation of vinyl triphenyl-



Scheme 30. Some examples of successful I–Sn exchange in vinyl triphenylstannane systems using either I_2 or NIS in CH_2Cl_2. Demonstration that Pd(0)-catalysed Stille, Sonogashira and Negishi cross couplings are possible with the vinyl iodides that result.[32]



Scheme 31. Some further examples of successful I–Sn exchange reactions, this time, in vinyl triphenylstannane systems with *cis* β-branching and a proof that Pd(0)-catalysed carbonylative and Suzuki cross couplings can be effected fairly readily in most cases.[32,30]

stannane **92** (Scheme 30), whose product **189** showed itself to be a viable partner for a highly challenging sp^3–sp^2 Stille cross coupling reaction with tetramethyltin, mediated by $PdCl_2(MeCN)_2$ in DMF at 100 °C under Farina's Ph_3As conditions, which typically bring about significant rate accelerations in such coupling processes. In this instance, application of this tactic led to **190** being formed in 70% yield[32] and, significantly, this type of allylically oxygenated

trisubstituted alkene is found in many bioactive natural products. Significantly as well, our application of the NIS method in this system actually gave an even higher yield of **189** than did our original I_2 protocol.

A similar success was recorded with **98** to obtain **191** whose Negishi cross-coupling was investigated with the commercial chiral organozinc bromide **192** shown in Scheme 30,[32] which furnished **193** in a rather modest 37% yield, due to the competing occurrence of a Zn–I exchange, which presumably occurred at a faster rate than the corresponding oxidative addition of the Pd(0)-complex, despite the latter being present at high loading. Nonetheless, if one thinks about alternative ways of rapidly accessing a complex stereodefined alkene such as **193** with high stereocontrol, one is left pondering, and so a 37% yield does not seem quite so bad in hindsight, when one considers what has been achieved and the alternatives currently available.

All of the examples of I–Sn exchange and subsequent Pd(0)-mediated cross coupling in Scheme 30 were performed on (*Z*)-vinylstannanes that lacked double carbon branching in the *cis*-related β-alkyl side chain. To answer the question of whether the presence of such an extra carbon branch point would perturb, or even totally prevent, I–Sn exchange and subsequent cross coupling, we investigated such processes in the examples presented in Scheme 31.[32]

Our first foray in this direction involved the vinyl triphenylstannane **120**.[32] This system was designed to be the prototypical test case that would provide all of the key answers as to whether further effort and expansion of scope would be possible. To our delight, the I–Sn exchange reaction on **120** proceeded smoothly and delivered **195** in 83% overall yield after O-silylation. The latter protection was done to specifically investigate whether a Pd(0)-catalysed carbonylation could subsequently be achieved cleanly in a system that had even more steric crowding around the vinyl iodide undergoing oxidative addition with the Pd(0). As can be seen from the sequence, the carbonylative conversion of **195** into **196** went cleanly enough, and gave **196** as a single product in 55% yield.

With this success behind us, we were now curious to see whether we could perform an I–Sn exchange on a branched β-arylated vinyl triphenylstannane, and a subsequent Pd(0)-mediated sp^3–sp^2 Stille cross coupling with Me_4Sn under our previously identified Farina conditions. It transpired that both processes worked satisfactorily, but the cross coupling reaction did proceed much more slowly on **197** (16 h at 100 °C) than it did on **189** (which only took 3 h to reach completion at 100 °C); the new cross coupling also proceeded in a lower yield (52%) than the corresponding one with **189** which proceeded in 70% yield.[32] Nevertheless, this outcome did put down a marker indicating what could potentially be done with iodostyryl systems.

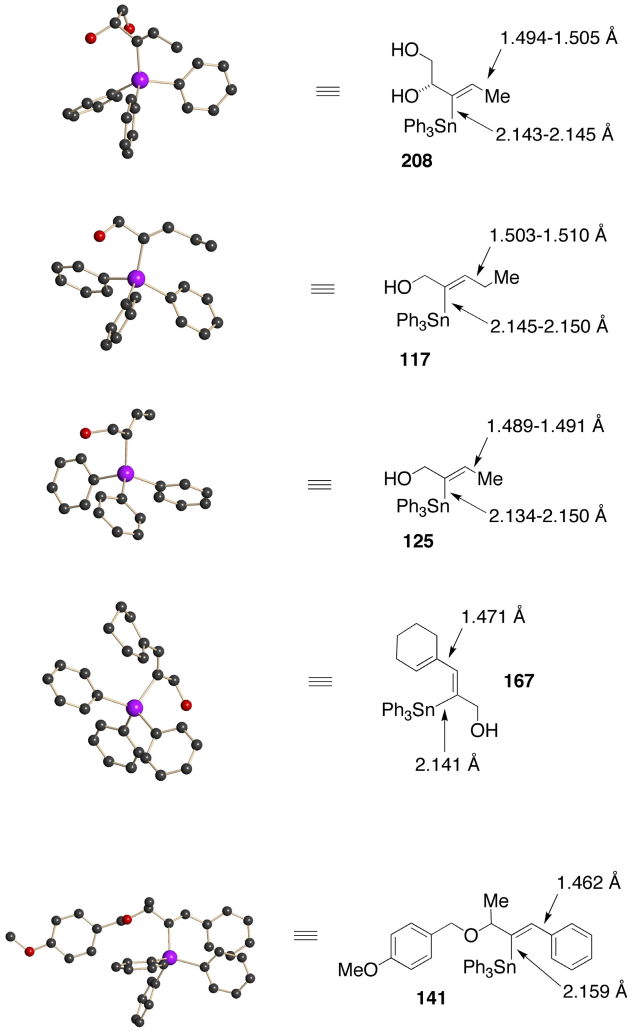
The next problem that we addressed was whether it would be possible to perform Suzuki couplings in this type of β-branched trisubstituted iodoolefin system, and accordingly vinyl iodides **199** and **202** were prepared, and their Suzuki couplings studied. As can be seen from Scheme 31,[32] such couplings were successful, and they generally proceeded in good yield.

Moreover, protection of a primary allylic hydroxyl was not always a requirement for success when this type of feature was present.

Naturally, all of these many victories in the vinylic I–Sn exchange reaction in the non-hindered primary and secondary allylically oxygenated trisubstituted vinyl triphenylstannane systems deserves further comment, most especially given all of the prior failures in the hindered or strongly internally-O-coordinated vinyl triphenylstannane systems outlined in Schemes 27 and 28.

In order to gain some mechanistic insights into the possible origins of this dichotomous behaviour, we examined carefully the X-ray crystal structures that we had determined[29] for the vinyl triphenylstannanes **208**, **117**, **125**, **167**, and **141** and all had a tetrahedral Sn atom (Figure 2). In none of these molecules could we find any evidence for strong or even weak internal coordination between the vinylic Sn atom and the allylic O-atom, which was not the case with **71**, **174** and **176** where the tertiary-OH had always been found to be engaged in a strong O–Sn interaction, with the Sn being trigonal bipyramidal. This was important since it provided a major point of difference between the two types of vinylstannane. It revealed that in non-hindered vinyl triphenyl-stannanes such as **208**, **117**, **125**, **167** and **141** where no internal O–Sn coordination occurs with the primary or secondary O-atom, the alkene component is always more electronically reactive and nucleophilic than the arene moiety, with the result that the alkene preferentially attacks the I_2 or NIS to give a hyperconjugatively stabilised β-stannylcarbocation that subsequently eliminates Ph_3SnX with the nucleophilic assistance of X^- ion in the manner shown in Scheme 32. The I–Sn exchange reaction proceeds with net retention of configuration as is typical for an electrophilic *ipso*-substitution.

Contrastingly, when one places severe steric encumbrances in the allylic positions around the vinyltin C=C double bond, and there is strong internal coordination of the allylic O-atom to the Sn atom to make the Sn take on a distorted trigonal bipyramidal shape (and also bear a formal negative charge), then one sees the balance of nucleophilic power shifting very dramatically in favour of the now more accessible apical phenyl component. Indeed, an inspection of Willem and Gielen's X-ray crystal structure of **174**[18] reveals that both the top and bottom sides of the alkene are very strongly sterically shielded by the equatorial phenyl groups of

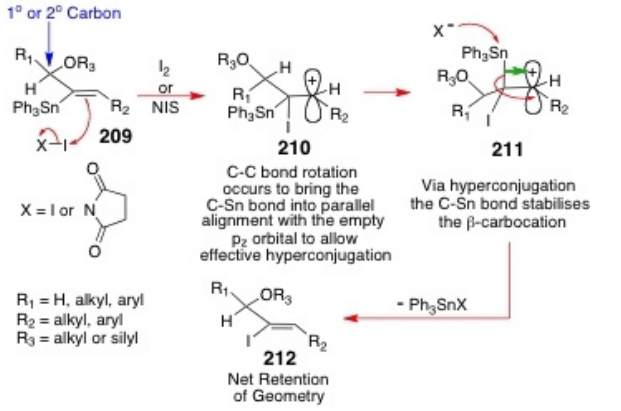


P. DImopoulos, J. George, D. A. Tocher, S. Manaviazar and K.J. Hale *Org. Lett.* **2005**, *7*, 5377 (Supporting Information).

Figure 2. The X-ray crystal structures of **208**, **117**, **125**, **167** and **141** all reveal that there is no internal Sn–O interaction. The lack of valence expansion for Sn, along with low steric hindrance around the C=C bond allows for I–Sn exchange to preferentially occur on the alkene to give the vinyl iodide in most systems.[29]

the Ph_3Sn moiety, and this arises because of the strong internal coordination restricting the free rotation of the *exo* C–Sn bond emerging from the alkene. As a consequence, the longer apical C–Sn bond is rendered more reactive and nucleophilic, and it is also now more readily approached by the I_2.

Under such circumstances two possible mechanisms can be envisaged for attack of the triphenyltin component on the I_2. Either an S_E2 type displacement proceeds on an I_2–Ph charge-transfer complex with the Ph_3Sn group, that commences with an attack of the C–Sn covalent bond on the I_2



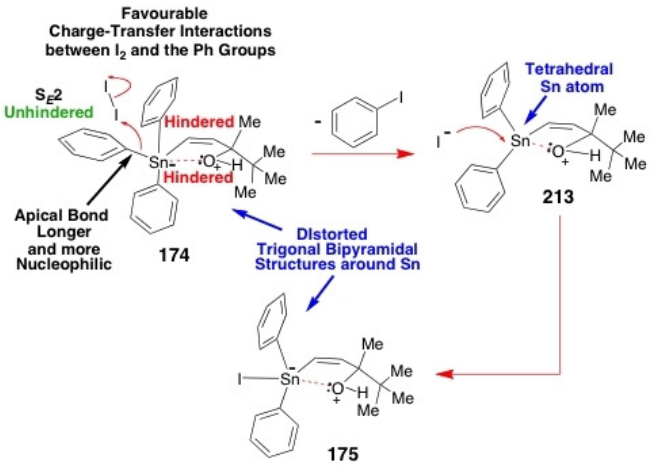
Scheme 32. The normal mode of I–Sn exchange in non-hindered vinyl triphenylstannane systems **209** where internal O–Sn coordination is absent and the Sn atom is tetrahedral.

(Scheme 33). This cleavage process would be completed by a second nucleophilic attack on the tetracoordinate Sn intermediate by the liberated I^-. Alternatively, a classic *ipso* electrophilic substitution by the I_2 can operate (Scheme 34), again accelerated by the negative charge on the tin. In the latter scenario, the phenyl ring would first nucleophilically attack the I_2 to generate a carbocation that would be hyperconjugatively stabilised by the C–Sn bond. Liberated I^- would then attack the Sn to complete the cleavage of C–Sn bond with loss of iodobenzene.

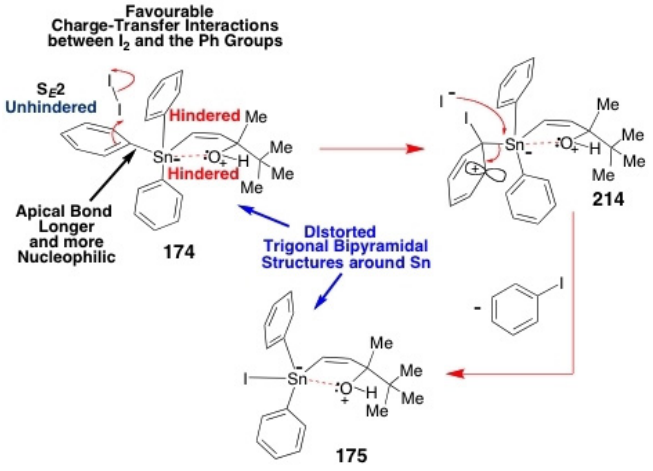
In our opinion, the former S_E2 process (Scheme 33) looks to be the more favourable in the **174**-type systems because it offers the most direct and least sterically congested pathway to the vinyl iodo(diphenyl)tin product **175**.

So, to summarise, primary or secondary allylically oxygenated trisubstituted vinyl triphenylstannanes that do not suffer from strong steric hindrance around the C=C bond will typically undergo I–Sn exchange with great felicity and high efficiency using I_2 or NIS, and they will always do so with retention of configuration (Scheme 32) possibly via the tentative mechanisms shown. The product vinyl iodides will also readily undergo a range of Pd(0)-mediated cross coupling reactions without undue problem (Schemes 30 and 31).

We will return to the issue of I–Sn exchange in sterically hindered vinyl triphenylstannane systems very shortly in the context of our discussions of the synthetic work that we have performed on (−)-(3*R*)-inthomycin C and (+)-acutiphycin, where severe steric encumbrances around the vinylstannane units forced us to modify our original I–Sn exchange reaction tactics in favour of a new set of experimental conditions that have proven excellent in atypical extreme circumstances of this sort. However, for the vast majority of synthetic situations such "force majeure" tactics are not usually required.



Scheme 33. Highly hindered, strongly internally O-coordinated, disubstituted vinyl triphenylstannanes e. g. **174** usually undergo Ph–Sn cleavage in preference to vinyl-Sn cleavage during I–Sn exchange reactions. Possibly this exchange occurs via the S_E2 pathway depicted here when there is strong internal O–Sn coordination or restricted rotation of the Ph_3Sn group, and the alkene is rendered too hindered to allow the I_2 to readily approach from either face. The negative charge on Sn would favour such an S_E2 type attack.



Scheme 34. The alternate *ipso*-substitution mechanism for formation of **174**. This would suffer from enhanced steric repulsions and a disruption of aromaticity. In our view, the alternative in Scheme 33 looks the more reasonable.

4. Applications of the Hale-Manaviazar-Willem-Gielen O-Directed Free Radical Hydrostannation Reaction of Propargylically-Oxygenated Dialkyl Acetylenes in Complex Natural Product Synthesis

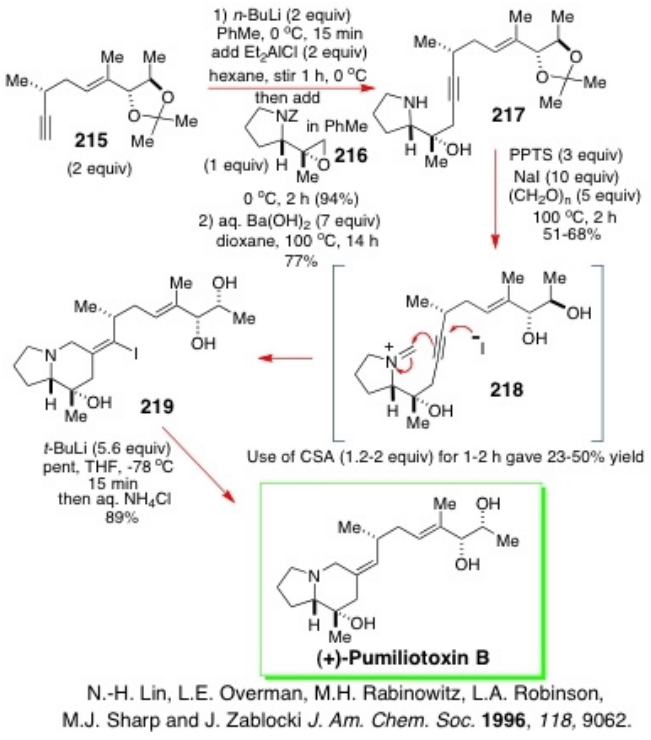
For many in the organic chemistry world, ourselves included, the only true test of new reaction utility is when a protocol is successfully deployed in a complex natural product total synthesis setting. The effective usage of new synthetic methods on this uncompromising stage not only helps to define the great power of particular procedures in complicated situations, it also helps to reveal the shortcomings and pitfalls of those methods. This, in turn, can lead to further methodological improvements that counter the unforeseen difficulties or failings that have arisen.

4.1. Formal Synthesis of (+)-Pumiliotoxin B

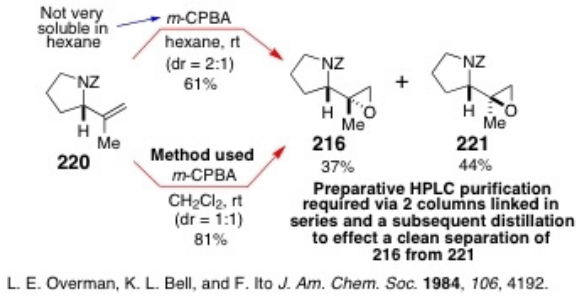
Given the great confidence that we had in our newly developed alkyne hydrostannation technology and its attendant alkene elaboration methods, we naturally wished to deploy them on an appropriate target molecule total synthesis problem, and the molecule that we initially selected as a suitable test vehicle was the frog alkaloid, (+)-pumiliotoxin B.

It transpired that this target molecule had already been synthesised twice by Larry Overman and his team (Scheme 35)[40] with their second effort featuring a very beautiful iodide/PPTS-promoted-alkyne-iminium ion cyclisation reaction on **217** to construct the indolizidine ring system (Scheme 35).[40a] In turn, that key precursor was constructed via an anionic union of the two fragments **215** and **216**, allied with a most unusual high temperature deprotection of the Z-group with excess $Ba(OH)_2$ in aqueous dioxane. A significant impediment in an otherwise excellent synthesis was the lack of stereocontrol observed in the key *m*-CPBA epoxidation step that was used to obtain **216**,[40b] which was accompanied by the formation of an equal amount of the unwanted *anti*-epoxide diastereoisomer **221** (Scheme 36). What made this issue particularly problematical was the fact that **216** and **221** both have an identical R_f on TLC which means that **216** is chromatographically inseparable by conventional SiO_2 flash chromatography. Although the stereoselectivity of this epoxidation step could be improved marginally by the use of hexane as the reaction solvent, this did not represent a practical solution to the problem at hand, since *m-CPBA* is not very soluble in this reaction solvent. Thus, the CH_2Cl_2 epoxidation procedure was the one that was ultimately used.

The removal of this unwanted epoxide **221** from **216** is by no means a trivial task for anyone attempting to repeat this synthesis, since it requires a highly labour intensive preparative HPLC procedure to effect separation; one that uses two HPLC columns linked in series, and a subsequent bulb-to-bulb distillation to allow the final compound to be separated. Overall, these tasks require considerable effort and skill, if they are to be done successfully, and clearly this separation problem is a major impediment to high material throughput. Indeed, as Overman himself states in his 1984



Scheme 35. Overman's masterly endgame for (+)-pumiliotoxin B, and his discovery that PPTS/NaI was the optimal reagent system for cyclisation.[40a]



Scheme 36. Overman's epoxidation route to epoxide **216**,[40b] and its dependence on a double preparative HPLC separation and bulb-to-bulb distillation to secure pure **216**.

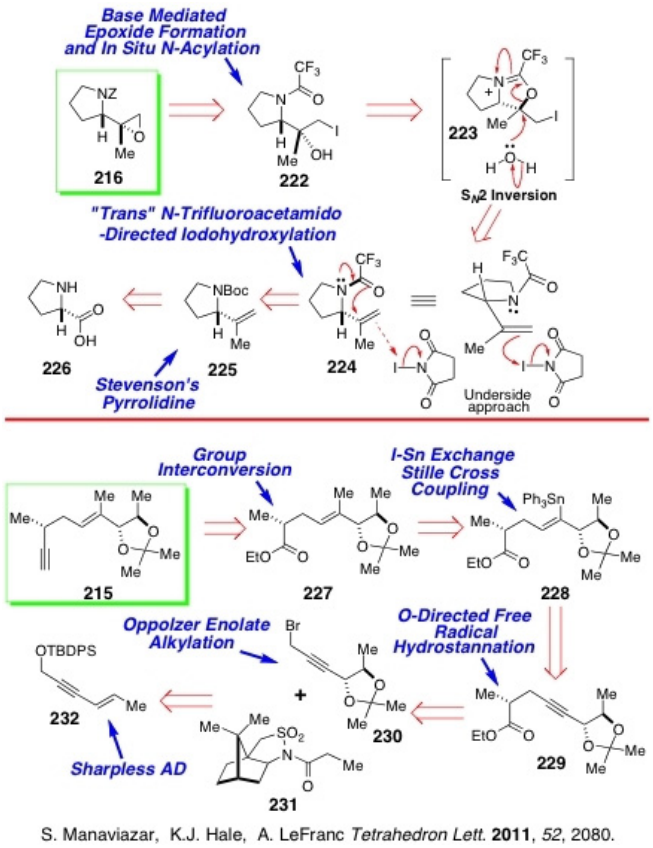
JACS report[40b] on the synthesis of **216** from **220**: *"Clearly, room for improvement remains in this epoxidation step"*.

Given this background, we decided to try to formulate a new and greatly improved formal total synthesis of (+)-pumiliotoxin B[41] that would make the existing second-generation Overman synthesis far easier to carry out. Our aim was still to rely on Overman's superb endgame, which really was quite spectacular, but to render the earlier stages of that synthesis far more practical and convenient. In this context, we wished to give greatly improved access to his two intermediates **215** and **216** and to totally dispense with the difficult double preparative HPLC separation and bulb-to-bulb distillation that was impeding convenient access to epoxide **216**.

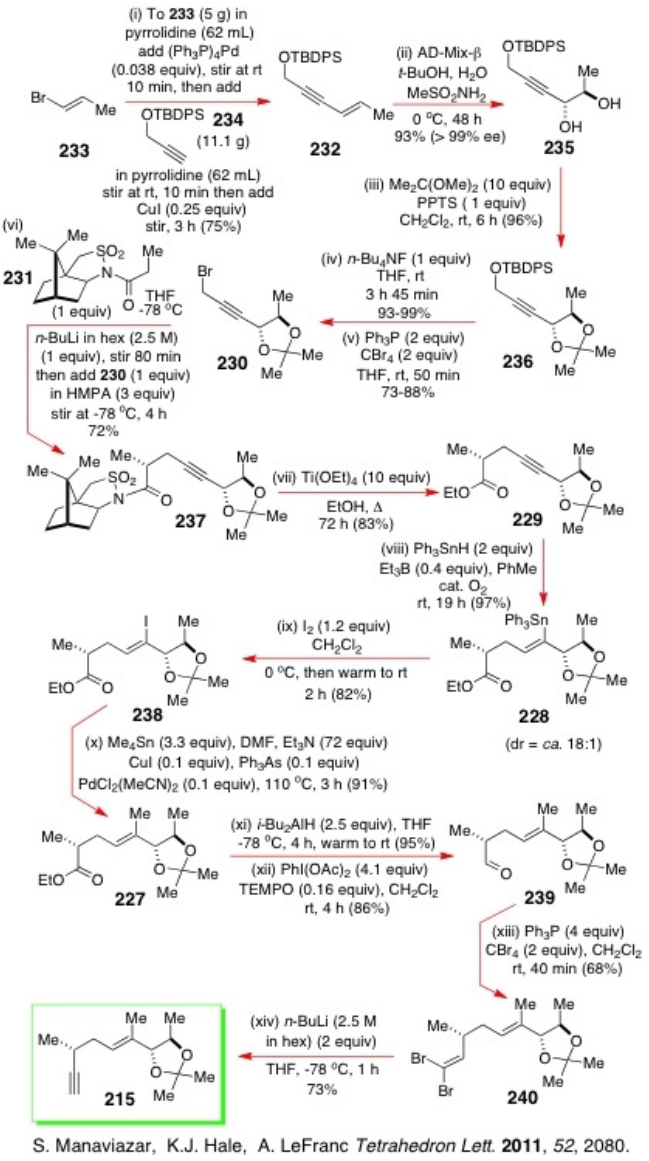
It was the presence of the allylically oxygenated trisubstituted alkene side chain in (+)-pumiliotoxin B that initially attracted us to this particular target, since this looked ideally suited to efficient construction by the Hale-Manaviazar-Willem-Gielen rt O-directed free radical alkyne hydrostannation reaction.[23,21] However, it was only when we carefully studied the previous synthesis in detail, and we ourselves attempted to independently obtain the epoxide **216**, via the published route, that we became fully aware of the true magnitude of the separation difficulties that attend its synthetic acquisition.

Accordingly we formulated a new retrosynthetic plan for the synthetic obtention of **215** and **216**, and this is detailed in Scheme 37.[41] In this, a novel *trans* N-trifluoroacetamido-directed iodohydroxylation reaction on **224** would be used to create the chiral iodohydrin **222**, which we envisioned would be directly convertible into **216** by a simple treatment with dilute NaOH and benzyl chloroformate. The predicted stereochemical outcome of this iodohydroxylation event was based upon the proposal that the most populated conformer of **224** would likely be the one where the isopropenyl group bore a *trans*-relationship to the N-trifluoroacetamido group, to avoid the steric clashes that would otherwise be encountered between these groups when they sit *syn* to one another and, as a result, we predicted that this would lead to the trifluoroacetamido group sterically blocking the top face of alkene, to force a reaction with the I^+ reagent from the alkene underside. Although previously unprecedented, we envisioned that neighbouring group participation from the N-trifluoroacetamido group would inevitably occur, to give the oxazolium intermediate **223**, which would undergo external S_N2 attack by H_2O in the manner shown, to set the desired tertiary alcohol stereochemistry. A major advantage of success in this approach would potentially lie in the ease of removal of the N-trifluoroacetamido protecting group from the product post iodohydroxylation, which would clearly be a most useful reaction advance of potentially wider significance. Alkene **225** would itself be prepared from (*S*)-proline **226** via Stevenson's very reliable procedure.[42]

For alkyne **215**, we imagined that it could be derived from the ester **227** by standard functional group interconversions. The key transformation needed to access **227** would be the O-directed free radical hydrostannation that would be effected on the alkyne **229** to obtain **228** which, thereafter, would be advanced through to **227** by I–Sn exchange and Stille cross coupling with Me_4Sn, under our now standard conditions for sp^3–sp^2 union.[32] The next question that needed to be addressed was how could we install the requisite Me stereocentre within **229**? In the end, we opted for an Oppolzer asymmetric alkylation between the propargyl



Scheme 37. The Hale-Manaviazar retrosynthetic plan[41] for the synthetic obtention of Overman's advanced synthetic intermediates **215** and **216** that had previously been used in his synthesis of (+)-pumiliotoxin B.



Scheme 38. The Hale-Manaviazar O-directed alkyne hydrostannation pathway to Overman's (+)-pumiliotoxin B alkyne **215**; its longest linear sequence was shorter than the route reported previously.[41]

bromide **230** and the lithium enolate derived from the camphorsultam propionamide **231**. The *syn*-relationship between the two oxygen stereocentres in **230**, along with Sharpless' report that enynes are excellent substrates for asymmetric dihydroxylation (AD),[43] suggested that this device, applied on **232**, would set the two key stereocentres present in **230** with great efficiency. A possible advantage of following this particular approach would derive from the convenience of the subsequent conversion of the product diol into the requisite bromide **230**.

Accordingly, we commenced our efforts on the preparation of alkyne **215**. Initially, we performed a Sonogashira coupling between the protected alkyne **234** and 1-bromo-1-propene (**233**) (Scheme 38) to access **232** in 75% yield. The Sharpless AD[43] that followed also performed admirably furnishing the diol **235** in high yield (93%) and superb ee (>99%). O-Isopropylidenation next afforded **236** which was O-desilylated with TBAF and brominated with Ph_3P/CBr_4 in THF; both steps were high yielding. Oppolzer alkylation with the lithium enolate derived from **231** proceeded smoothly over 4 h in the presence of HMPA to afford **237** as the sole reaction product in 72% yield. To avoid potential problems with a loss of stereochemical integrity at the newly introduced Me-stereocentre, we detached the auxiliary from **237** by transesterification with $Ti(OEt)_4$ in EtOH at reflux; this reaction proceeded in 83% yield and furnished **229** in stereochemically pure condition.

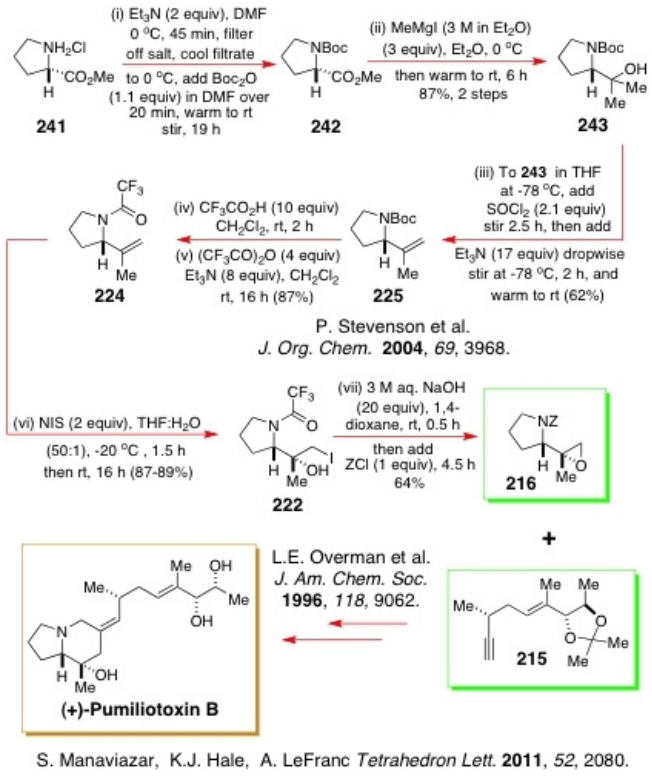
The key O-directed free radical hydrostannation was now implemented on **229** with Ph_3SnH and cat. Et_3B/O_2 in PhMe at rt. It performed very well indeed, furnishing **228** as the major component of an 18:1 mixture of diastereomers in 97% yield. Because the vinyl triphenylstannane in **228** was

not especially hindered, it readily underwent I–Sn exchange under our standard reaction conditions which use 1.2 equiv. of I_2 in CH_2Cl_2. The product vinyl iodide **238** was isolated as a single diastereomer in 82% yield, and it readily engaged in a Stille cross coupling with Me_4Sn under our established high temperature Farina Ph_3As promoted conditions[44] which use $(MeCN)_2PdCl_2$ as the catalyst. Having secured **227** in 91% yield, without any loss of stereochemical integrity, we next reduced its ester to a primary alcohol and oxidised this to the aldehyde **239**. It has to be said that this oxidation step initially proved to be most troublesome, with the vast majority of oxidants that we evaluated causing significant epimerisation of the α-methyl stereocentre (e.g. Me_2SO/$(CF_3CO)_2O$/CH_2Cl_2/Et_3N at −78 °C). Fortunately, we had already encountered a similar problem in our (+)-eremantholide A synthesis[45] and, in the end, how we overcame this issue was to use catalytic TEMPO and excess stoichiometric iodobenzene diacetate in a Piancatelli oxidation. This nicely solved the problem at hand as well, affording **239** without any loss of α-methyl stereocentre integrity.

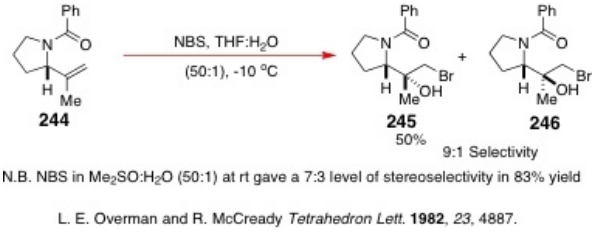
Notwithstanding us now being fully aware of the extreme sensitivity of the Me-stereocentre in **239** towards base mediated epimerisation, we nonetheless attempted to directly introduce the alkyne unit of **215** directly using the Ohira-Bestmann reagent and K_2CO_3 in MeOH. As expected, it furnished the expected alkyne, but the propargylic-Me had undergone substantial epimerisation! We therefore had to rely on the trusty Corey-Fuchs two step method of alkyne elaboration, which delivered the desired alkyne **215** from the dibromoolefin **240** in high overall yield without any problems.

Thus, the first leg of our (+)-pumiliotoxin B journey was over, and the great worth of the Hale-Manaviazar-Willem-Gielen O-directed free radical hydrostannation reaction[23,21] had been demonstrated in a formal total synthesis setting, as had our allied Hale-Manaviazar trisubstituted olefin elaboration technologies.[32]

Even so, the highly challenging synthesis of epoxide **216** still lay ahead. In the end, this proved to be quite a simple task when we followed our newly planned route (Scheme 39), which worked very well indeed, in no small part due to its reliance on Stevenson's excellent pathway to the chiral pyrrolidine **225**,[42] and on an earlier key observation made by Overman and McReady[40c] in their bromohydroxylation of the N-benzoyl pyrrolidine analogue **244** in 1982 (Scheme 40). These two workers had previously found that this reaction on **244** furnished **245** with 9:1 stereoselectivity in favour of the desired tertiary alcohol product when conducted in THF:H_2O (50:1) at −10 °C. However, they were subsequently outflanked and unable to capitalise on this outstanding result, due to the insurmountable difficulties that they encountered in non-destructively cleaving the N-benzoyl



Scheme 39. Our new *trans*-trifluoroacetamido-directed iodohydroxylation reaction and how it was used to stereoselectively synthesise the chiral epoxide **216** and thus complete a new and highly convenient formal total synthesis of (+)-pumiliotoxin B with high stereocontrol.[41]



Scheme 40. Overman and McCready's earlier attempt at bromohydroxylating the alkene **244**. Unfortunately, they were unable to manipulate **245** into **216**.[40c]

group from their purified product **245** in their subsequent efforts to convert it into **216**. In the end, this meant that they were forced to abandon this most useful approach, and pursue the alternate route shown in Scheme 36 with all of its attendant difficulties.

If we return now to our own synthesis of **216** (Scheme 39), we commenced it with a repetition of Stevenson's extremely reliable route to **225**,[42] which entailed taking commercially available **241** and introducing a Boc-protecting group onto the ring nitrogen to access **242**, which was

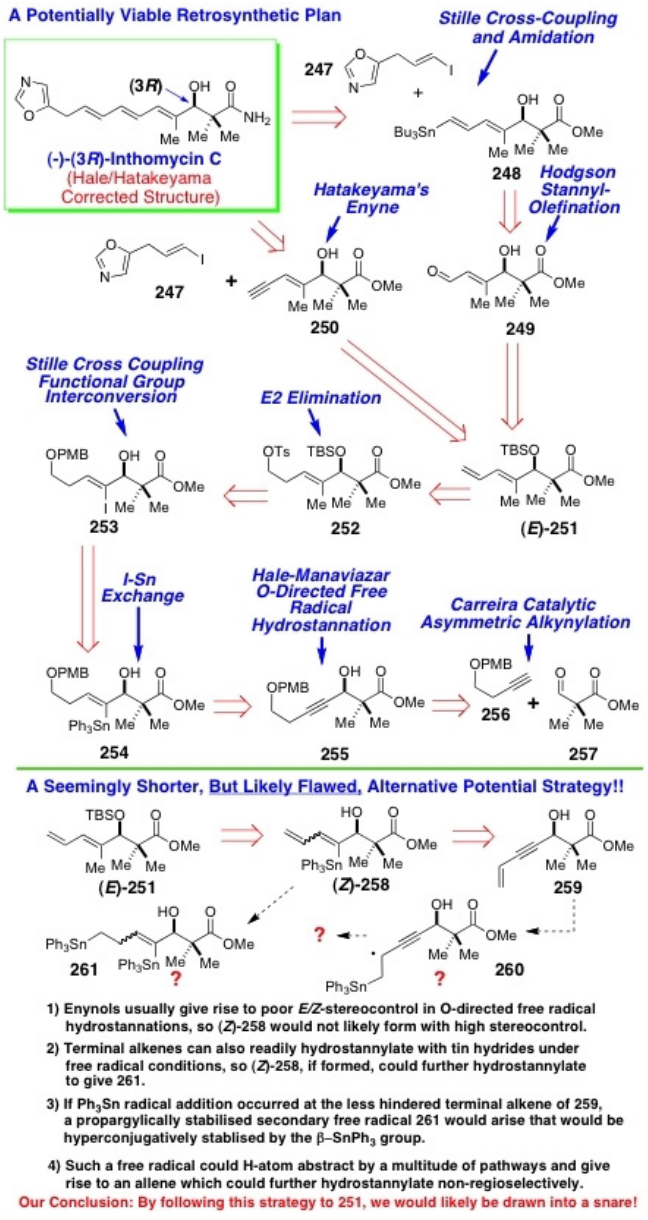
converted into **243**; the latter was then dehydrated with thionyl chloride/Et_3N. With **225** in hand, we could now convert it into **224** and examine the aforementioned *trans*-N-trifluoroacetamido-directed iodo-hydroxylation reaction with NIS in THF/H_2O at −20 °C, which gave rise to the predicted product **222**. In this respect, *ca.* 12 : 1 selectivity was typically encountered in favour of **222**. While we ourselves believe that this outcome reflects the occurrence of neighbouring group participation in the manner shown in Scheme 37, a referee of the present article has suggested an equally viable alternative that we present in the Footnotes and References section.[46] Base treatment of **222** with 3 M aqueous NaOH then furnished the desired epoxide, and concurrently deprotected the N-trifluoroacetamido group to liberate the chiral pyrrolidine, which was N-acylated *in situ* with benzyl chloroformate to ultimately afford pure **216**.

This formal synthesis of (+)-pumiliotoxin B[41] thus constituted the first successful deployment of the O-directed alkyl acetylene free radical hydrostannation reaction in natural product total synthesis, and it cut down the overall number of synthetic steps needed to arrive at Overman's advanced alkyne **215**. Our synthesis also demonstrated the great worth of the N-trifluoroacetamido group in directing the course of the alkene iodohydroxylation reaction, we believe, when it is used in an appropriate olefinic setting. As such, it showed that the N-trifluoroacetamido group can potentially function as a participatory neigbouring-group when called upon to do so. Our combined synthetic contributions[41] have thus helped to greatly improve Overman's second-generation total synthesis of (+)-pumiliotoxin B[40] to make it more practical from a material throughput perspective.

4.2. Total Synthesis of (−)-(3*R*)-Inthomycin C

Another target molecule that caught our eye for a potentially pivotal demonstration of the utility of the Ph_3SnH/cat. Et_3B/O_2 O-directed free radical hydrostannation reaction in a highly hindered environment was (−)-(3*R*)-inthomycin C.[47]

We therefore put together the retrosynthetic plan shown in Scheme 41 for the synthetic obtention of (−)-(3*R*)-inthomycin C.[48] A key element of our approach was the use of Ryu's earlier endgame[49] for completing the total synthesis from the vinyl iodide **247** and the dienylstannane **248**, via Baldwin/Lee/Stille cross coupling;[50] the latter union would be allied with a saponification and amidation to arrive at the target. Our preferred plan for obtaining **248** would apply a Hodgson stannyl-olefination[51] to **249** which itself would be derived from the (*E*)-diene **251** by O-desilylation and regioselective oxidative cleavage of the terminal olefin. The latter would be obtained from **252** by E2 elimination. We envisioned securing the O-tosylate **252** from the vinyl triphenylstannane **254** by I–Sn exchange to access **253**, Stille



Scheme 41. The Hale-Manaviazar retrosynthetic planning for (−)-(3*R*)-inthomycin C and our rejection of the radical hydrostannation of **259**.[48]

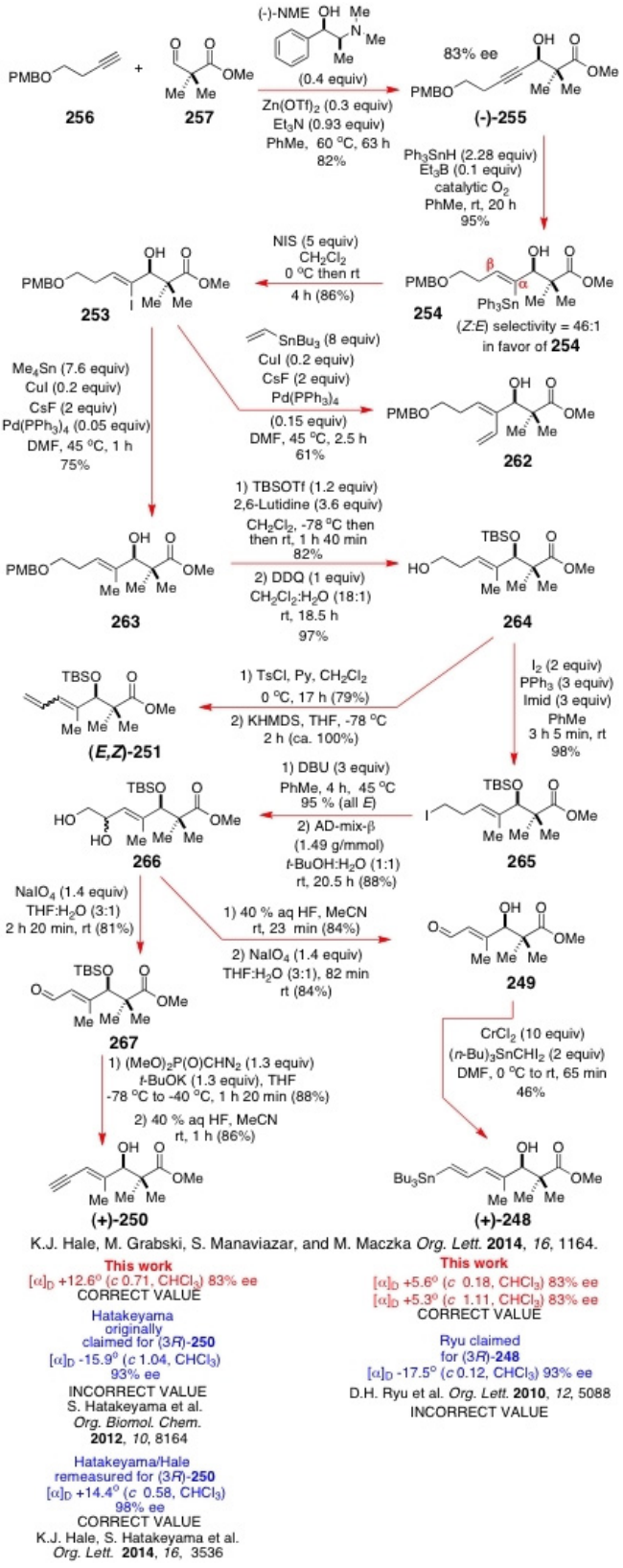
cross coupling and through further manipulation of the terminal OPMB group. Naturally, **254** would derive from an application of the Hale-Manaviazar-Willem-Gielen O-directed free radical hydrostannation reaction[23,21] on **255**, which itself would be assembled through the catalytic Carreira asymmetric alkynylation of **257** with **256**.[52]

Importantly, this would be the first time the O-directed free radical hydrostannation process had ever been applied on a propargylic alcohol substrate with an all-carbon β-quaternary C-centre. The presence of the geminal dimethyl group

would also pose a particularly important test for the subsequent I–Sn exchange and Stille cross coupling reactions, since the like of such reactions had never previously been reported in the literature. So, not only was this synthetic problem an important test of our hydrostannation technology, it would also further scrutinise the protocols that we had introduced for alkene elaboration, and find out whether they were lacking in a much more sterically hindered setting. Strategically, we opted for the longer approach shown in Scheme 41, because the seemingly simpler one involving a direct application of the O-directed free radical hydrostannation to **259** was considered fraught with potential difficulties. This is because enynols often give rise to poor (*E*/*Z*)-stereocontrol in such processes due to their likely *linear* vinyl radical structures and their susceptibility to competing tin radical induced dienylstannane isomerisation at rt under the Et_3B/O_2 initiated conditions. Additionally, the terminal alkene present in the desired product (*Z*)-**258** could itself potentially undergo further hydrostannylation and give rise to the double hydrostannation product **261**; so too could the enynol **259**, but in an even more complex way. In this regard, terminal alkenes are well known to readily hydrostannylate, under free radical conditions, and so we could sense that the occurrence of such events either on (*Z*)-**258** or its potential precursor **259** could set in motion a multitude of competing radical hydrostannation pathways that could very quickly lead to multiple products, in some cases arising from allene intermediates. We considered this to be poor synthetic planning, and so we decided to avoid this potential snare by accessing **248** from **254** and **255**.

Accordingly, we began our synthesis[48] with the union of **256** and **257** under Carreira's catalytic asymmetric alkynylation conditions.[52] We found that his reported general procedure worked very successfully in this new system, furnishing the desired product **255** in high yield and 83 % ee (Scheme 42). Alkynol **255** was then immediately subjected to O-directed hydrostannation with Ph_3SnH/cat. Et_3B/O_2 in PhMe and gave the (*Z*)-vinyl triphenylstannane **254** as the major component of an inseparable 46 : 1 mixture in 95 % yield.

Only after extensive studies in this and related hindered systems, did we gradually realise that when one is dealing with sterically congested vinyl triphenylstannanes such as **254**, where the alkene is highly hindered, such systems will often only undergo vinylic I–Sn exchange efficiently when all of the phenyl groups have been cleaved from the Sn atom to give the less hindered vinyltin tri-iodide, which will then eventually undergo the requisite I–Sn exchange reaction to give the desired vinyl iodide in good yield. Fully appreciating this fact took us quite some time, but as soon as we did realise it, along with the fact that one must always use N-iodosuccinimide (and not I_2) for I–Sn exchange reactions



Scheme 42. Our formal syntheses of (−)-(3*R*)-inthomycin C.[48]

involving hindered vinyltin systems, eventually we made the key breakthrough needed to successfully convert **254** into **253** in good yield, in what was, in the end, an extremely clean reaction.

Whilst on this point, one of the primary problems that one typically encounters in the I–Sn exchange process in highly hindered vinyl triphenylstannane systems is in the TLC analysis of such reactions, since the vinyltin halide products typically have a very strong tendency to sit near to, or even at, the baseline, which is not the case for the starting vinyl triphenylstannanes. This can give an immediate and rather lasting false impression that extensive decomposition has occurred during the very early to mid-stages of the I–Sn exchange process. In the case of the NIS-mediated reactions, however, as time passes, one will eventually start to see the more polar baseline product(s) gradually disappearing, only to be replaced by a single much faster-moving product, that frequently moves faster than the original vinyl triphenylstannane itself, or has a quite similar TLC mobility to that precursor; this product is usually the vinyl iodide. We draw the community's specific attention to this most disconcerting TLC behaviour, to assist in the future evaluation of such reactions in other hindered settings. While this TLC behaviour is often the case with the NIS-mediated reactions, this cannot be said for the corresponding I_2 in CH_2Cl_2 reactions in hindered systems, where baseline decomposition products are frequently the norm, which contrasts strongly with the results one typically observes with I_2 in *non-hindered* vinyl triphenylstannane systems.

If we return now to the synthesis at hand, we next proceeded to examine the Stille cross-coupling of **253**, which was an unprecedented reaction at the time. We have usually found that hindered systems such as these, with a β-geminal dimethyl feature, generally do not cross couple under our originally developed standard Stille cross-coupling conditions, which use Farina's Ph_3As[44] as an additive. This is not the situation, however, when resort is made to the Baldwin-Lee variant[50] of the Stille cross coupling, which uses copper (I) iodide (0.2 equiv) as an additive, alongside CsF (2 equiv) and catalytic $Pd(PPh_3)_4$ (5 mol%) in the presence of excess stannane in DMF at 45 °C. In the present instance, with Me_4Sn, the desired coupling on **253** gave **263** in a very decent 75% yield. The analogous reaction with vinyl tributyltin likewise afforded the diene **262** in respectable yield, attesting to the generality of this new coupling protocol, above and beyond the one desired for inthomycin C. In our view, the Baldwin-Lee variant[50] of the Stille cross coupling is one of the outstanding reactions of modern-day synthetic organic chemistry.

With the synthesis of **263** behind us, we next pressed ahead with its conversion into **264** by O-silylation with TBSOTf and 2,6-lutidine, and O-debenzylation with DDQ. Both reactions proceeded smoothly. Thereafter, we attempted the conversion of **264** into the O-tosylate **252** and E2 elimination with KHMDS. Unfortunately, the latter reaction proceeded down the E1cb pathway rather than the E2 route we had intended, and it afforded a mixture of (*E/Z*)-geometric isomers of **251**. Further investigations eventually led to the iodide **265** emerging as the best precursor of (*E*)-**251** and 1,8-diazabicyclo[5.4.0]undec-7-ene emerging as the best base to induce its E2 elimination. The latter led to (*E*)-**251** exclusively in excellent yield.

A Sharpless AD reaction[43] now allowed the less hindered terminal alkene to be selectively dihydroxylated but the reaction was non-stereoselective. This step was followed by O-desilylation with 40% aq. HF in MeCN, and oxidative cleavage of the 1,2-diol with aqueous $NaIO_4$ in THF. This sequence cleanly delivered the enal **249** in good yield. The last step of this formal synthesis was a link up with Ryu's vinylstannane **248**[49] via a Hodgson-Takai Cr(II)-mediated stannylolefination,[51] which proceeded in modest yield, but it did so in the presence of a free hydroxyl. Despite this, workable quantities of (+)-**248** were able to be brought through. Pleasingly, the NMR spectrum of **248** matched that of Ryu.[49]

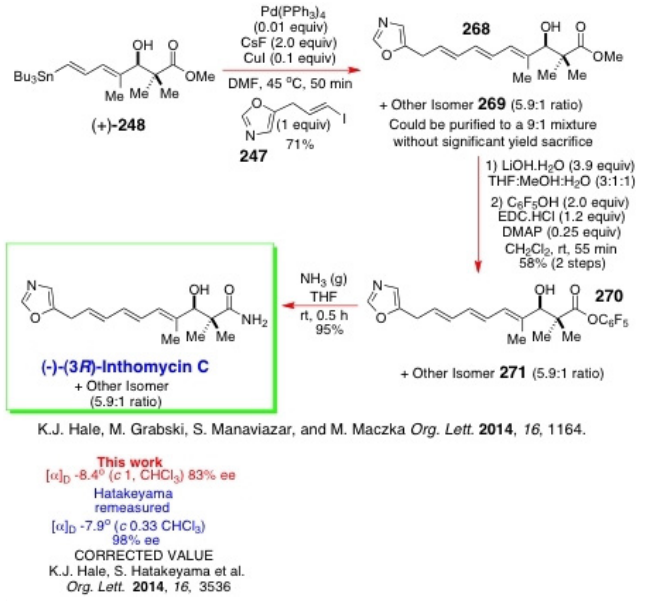
However, it was at this juncture that we encountered our first surprise, for when we measured the $[\alpha]_D$ value of our synthetic **248** of 83% ee, we found it to be of positive sign and of much lower magnitude than Ryu et al,[49] it being $+5.3^\circ$ (*c* 1.11 $CHCl_3$), which conflicted strongly with the negative value recorded by this team[49] for material of 93% ee (their $[\alpha]_D = -17.5^\circ$ (*c* 0.12, $CHCl_3$)). Clearly something was awry here, and to confirm that the absolute stereochemistry of our product was correct, we duly prepared the Mosher esters of (−)-**255** and our subsequent NMR analysis confirmed that its stereochemistry was as we had assigned it, and that nothing was amiss.

In order to resolve this discrepancy, we now decided to do a link up with the enynol **250** used in Hatakeyama's synthesis of (−)-(3*R*)-inthomycin C[53] and, accordingly, we prepared (+)-**250** by treatment of enal **267** with Shioiri's reagent $(MeO_2)P(O)CHN_2$ in THF in the presence of KOBu-*t*, to complete a second formal total synthesis. However, yet another surprise now befell us; our $[\alpha]_D$ of $+12.6^\circ$ (*c* 0.71, $CHCl_3$) was of similar magnitude *but opposite sign* to that reported by Hatakeyama et al.[53] This combined data very clearly indicated that Ryu[49] and Hatakeyama[53] had both apparently prepared the opposite enantiomer to that depicted for (+)-**248** and (+)-**250** in Scheme 42. Given this finding, and the fact that Taylor[54] had earlier reported that (3*R*)-inthomycin C of 76% ee, contaminated with 20% tetramethylurea, had a large positive $[\alpha]_D$ of $+25.9^\circ$ (*c* 0.27, $CHCl_3$), this seemingly confirmed that view, since Hatakeyama and Ryu had both reported large negative $[\alpha]_D$ values of

-41.5° (c 0.1, $CHCl_3$) and -34.3° (c 0.1, $CHCl_3$) for their versions of (−)-inthomycin C.

We therefore felt duty bound to convert our (+)-**248** into (3*R*)-inthomycin C and then do a rotational comparison to make sure that all was well there. Accordingly we repeated the exact Stille cross coupling reported by Ryu et al[49] (Scheme 43) and observed that a 5.9 : 1 mixture of geometric isomers was formed enriched in the desired product **268**. Ryu had reported that a single product had emerged from this process. However, this was not what we found, and we were never able to isolate a single geometric isomer from this reaction despite many repeats.

Eventually, after preparative TLC, we were able to purify our version of **268** to the point where it was a 9 : 1 mixture of geometric isomers without major material losses, but to obtain a more enriched 17.1 : 1 mixture, much greater material sacrifice had to be endured. To continue the synthesis, however, and explore a greatly improved endgame for the final three steps, we took our 9 : 1 mixture of isomers and duly hydrolysed the methyl ester, converting the resulting acid into the pentafluorophenyl ester **270**. We then ammonolysed with gaseous NH_3 dissolved in THF to obtain (3*R*)-inthomycin C as a 9.7 : 1 mixture of stereoisomers after chromatographic purification. To our great dismay, however, this purified sample, which had been concentrated from $CDCl_3$ following NMR analysis, subsequently broke down after being stored in the freezer over a period of weeks, before we were in a position to be able to measure its $[\alpha]_D$. We



Scheme 43. Our repetition of the Ryu inthomycin C cross coupling[49] to obtain **268** and our new improved endgame for reaching (−)-(3*R*)-inthomycin C.[48]

therefore repeated the new endgame with our 5.9 : 1 mixture enriched in **268** and obtained a similar mixture of (3*R*)-inthomycin C and this isomeric triene component. The $[\alpha]_D$ for this mixture was found to be of negative sign, and of low magnitude; -8.4° (c 1, $CHCl_3$) for material of 83% ee.

Given that Hatakeyama had reported a much higher $[\alpha]_D$ of -41.1° (c 0.1, $CHCl_3$) for pure (3*R*)-inthomycin C in 2012,[53] and Ryu had earlier recorded an $[\alpha]_D$ -34.33° (c 0.1 $CHCl_3$) for 93% ee material in 2010,[49] and Taylor had even earlier stated that (3*R*)-inthomycin C of 76% ee (contaminated with 20% tetramethylurea) had $[\alpha]_D$ of $+25.9^\circ$ (c 0.27, $CHCl_3$)),[54] we naturally concluded that we had prepared the (+)-enantiomer like Taylor, but our isomeric triene contaminent had been responsible for conferring the overall low negative $[\alpha]_D$ on our sample. We were led to this overall view by the $[\alpha]_D$ data that we had obtained on (+)-**248** and (+)-**250** which were clearly of opposite sign to the $[\alpha]_D$ values reported by Ryu and Hatakeyama for materials of unverified stereochemistry.

We further concluded that the Hatakeyama and Ryu teams must have both prepared unnatural enantiomeric (−)-(3*S*)-inthomycin C. We therefore duly published our conclusions[48a] thinking that all was well.

However, not long after our *Organic Letters* communique appeared,[48a] Professor Hatakeyama contacted us to inform us that he and his team had gone back through their lab records after seeing our report, and they had now found that they had mistakenly reported the $[\alpha]_D$ value of their sample of **250**. Rather than it being -15.9° as they had inadvertently quoted in their 2012 OBC paper (see Scheme 42),[53] this value should actually have been $+15.6^\circ$! Moreover, in order to further to confirm that result beyond any doubt at all, the Hatakeyama team then went ahead and actually re-synthesised (+)-**250** one more time, and on this occasion they measured their $[\alpha]_D$ as $+12.2^\circ$ (c 0.95 $CHCl_3$), which was very close to the $+12.6^\circ$ (c 0.71 $CHCl_3$) value that we had reported in our new 2014 paper. Professor Hatakeyama also very kindly sent us a pure sample of his team's newly resynthesised (+)-**250** for us to independently judge his claim, and when we ourselves measured the $[\alpha]_D$ of his sample on our polarimeter at QUB, we found it to be $+14.4^\circ$ (c 0.58, $CHCl_3$).[48b]

Following this newly reconfirmed result, Professor Hatakeyama and his team then decided to repeat their own synthetic endgame for (−)-(3*R*)-inthomycin C from (+)-**250** and they now obtained a much smaller $[\alpha]_D$ value of -7.9° (c 0.33 $CHCl_3$) for the pure (−)-(3*R*)-inthomycin C that they obtained, which clearly was much more in keeping the $[\alpha]_D$ value that we ourselves had observed for our 5.9 : 1 mixture of 83% ee ($[\alpha]_D$ value of -8.4° (c 1 $CHCl_3$)). Other additional correlations were performed by our two groups,[48b] and after critically considering all of the published evidence that had

been gathered to date, we eventually concluded that Ryu and Taylor had also synthesised (−)-(3*R*)-inthomycin C but, in the case of Ryu et al,[49] they had incorrectly reported their $[\alpha]_D$ values for **248** and (−)-(3*R*)-inthomycin C, and for Taylor,[54] his $[\alpha]_D$ value had been rendered positive by the presence of the tetramethylurea contaminent; a phenomenon already documented in the literature for other chiral molecules.

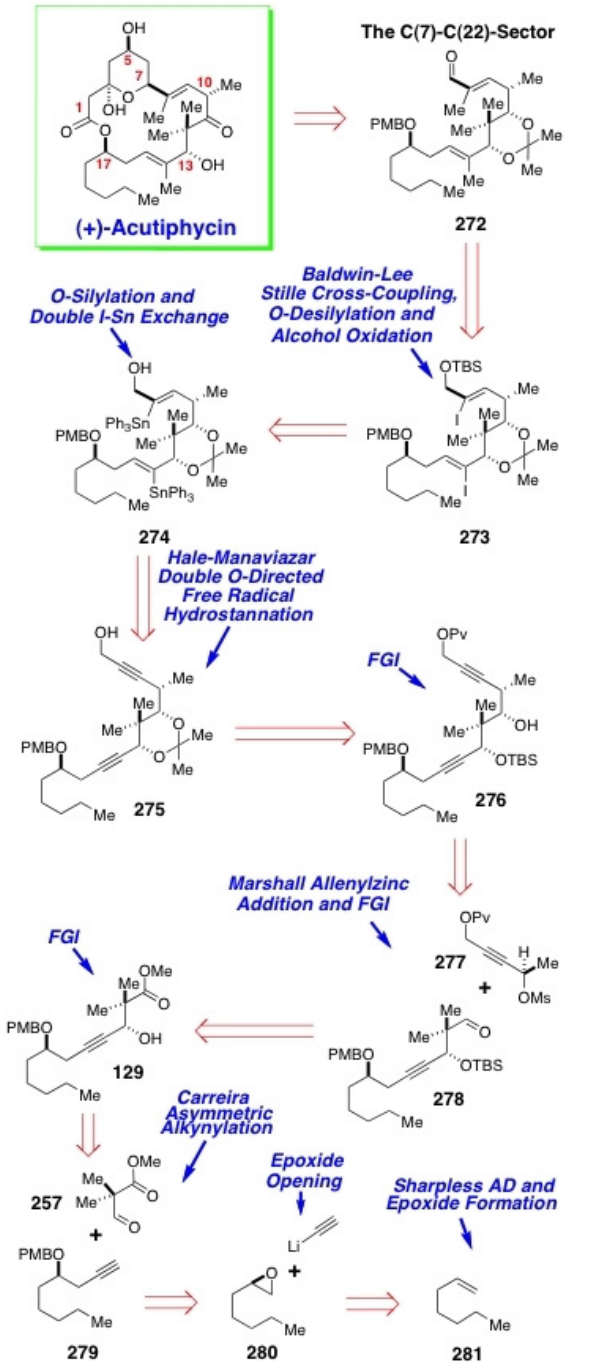
So, to conclude, and despite the title of our original 2014 paper stating that we had completed an asymmetric total synthesis of (+)-(3*R*)-inthomycin C,[48a] we had in actuality completed a synthesis of (−)-(3*R*)-inthomycin C,[48b] as our original $[\alpha]_D$ suggested, and we had thus powerfully confirmed the great utility of our O-directed dialkyl acetylene free radical hydrostannation reaction in a sterically demanding propargylic alcohol setting. We had also gained important new insights into how to do unprecedented I–Sn exchange reactions in hindered vinyl triphenylstannane systems and sp3–sp2 Stille cross couplings on equally demanding vinyl iodide products. Thus, much had been learned from this venture, and the utility of our new trisubstituted olefin synthesis had been clearly demonstrated beyond all doubt.

4.3. A Two-Directional Double O-Directed Alkyl Acetylene Free Radical Hydrostannation Approach to the Antitumour Macrolide (+)-Acutiphycin

Buoyed by the success of our O-directed hydrostannation methodology when applied in the (−)-(3*R*)-inthomycin C synthetic theatre,[48] we next set out to deploy a pioneering new two-directional *double* O-directed hydrostannation variant of our protocol on the highly hindered bis-propargylically oxygenated diyne **275** shown retrosynthetically in Scheme 44. We considered that the latter had all of the requisite functionality needed to allow a future asymmetric total synthesis of the antitumour macrolide, (+)-acutiphycin,[55] a natural product with interesting anticancer properties that is no longer available from its producing source.

The introduction of a new, higher-order, multiple O-directed free radical hydrostannation process for dialkyl acetylenes, that operated in highly hindered systems, would significantly expand the scope and likely future application of our new reaction in organic synthesis. Success in the subsequent alkene elaborations would also stand as a powerful testament to the future synthetic possibilities of the methodology and, for this very reason, we thought it essential that we successfully confront all of the issues and likely attendant problems that potentially lay ahead in the highly complex (+)-acutiphycin system.[56]

Accordingly, we duly formulated the retrosynthetic plan shown in Scheme 44 for the synthetic acquisition of the C(7)-C(22)-sectoral fragment **272** for our projected route to



Scheme 44. The Hale-Manaviazar retrosynthetic planning for the antitumour macrolide (+) acutiphycin. A new double O-directed free radical hydrostannation with Ph_3SnH/cat. Et_3B/O_2 would lie at its heart.[31]

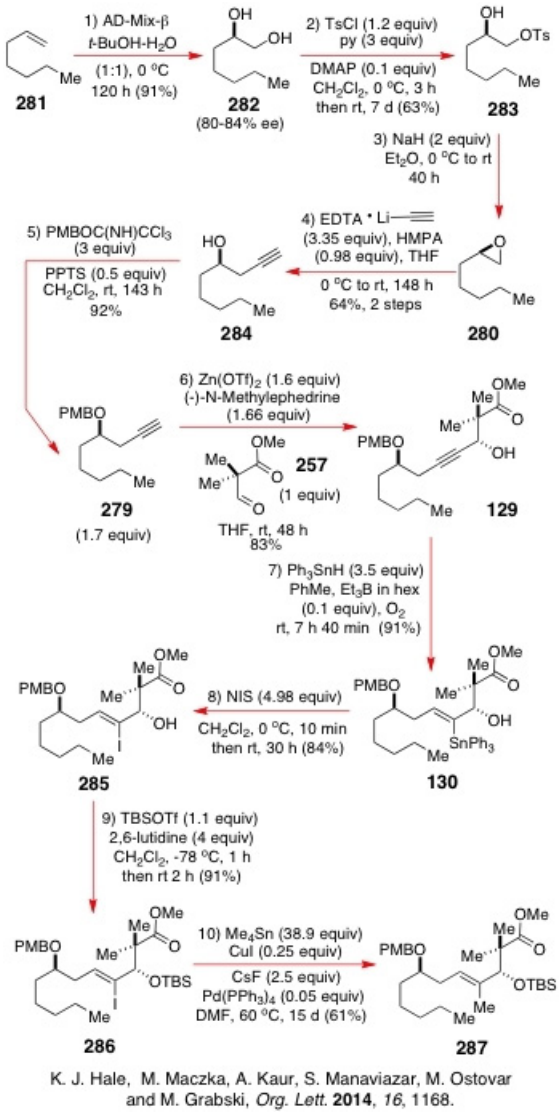
(+)-acutiphycin.[31] A key element of our design strategy was the deployment of a conformation-restraining O-isopropylidene acetal tether between the two acetylenic alcohol components of the diyne substrate **275**, to create a less sterically hindered O-director group at C(13) which we

believed would more readily promote the proposed double O-directed free radical hydrostannation in this highly hindered situation. We envisaged that the latter event would yield **274**, which could then be converted to **272** by successive I–Sn exchange, Stille cross coupling, and finally O-desilylation and oxidation. For the assemblage of **276**, the precursor of **275**, a Marshall chiral allenylzinc addition[57] was planned using the aldehyde **278** as a partner and the chiral propargylic O-mesylate **277** as the allenylzinc precursor, under Pd(0)-mediated conditions. Given our successes in the earlier (−)-(3*R*)-inthomycin C project, we again envisaged that a Carreira alkynylation[52] between **279** and **257** would suffice for the delivery of **129**, and to access the requisite acetylene partner, we envisioned an opening of the chiral epoxide **280** with lithium acetylide, allied with O-*p*-methoxybenzylation. In turn, the chiral epoxide **280** would be prepared on scale from a chiral 1,2-diol prepared via a Sharpless AD reaction[43] applied on **281** using the method of Smith et al.[56a]

Prior to embarking on our double O-directed free radical hydrostannation route in earnest, we thought it prudent to first of all evaluate whether we could successfully perform a rt mono-hydrostannation with Ph_3SnH/cat. Et_3B/O_2 upon the alkynol **129**.

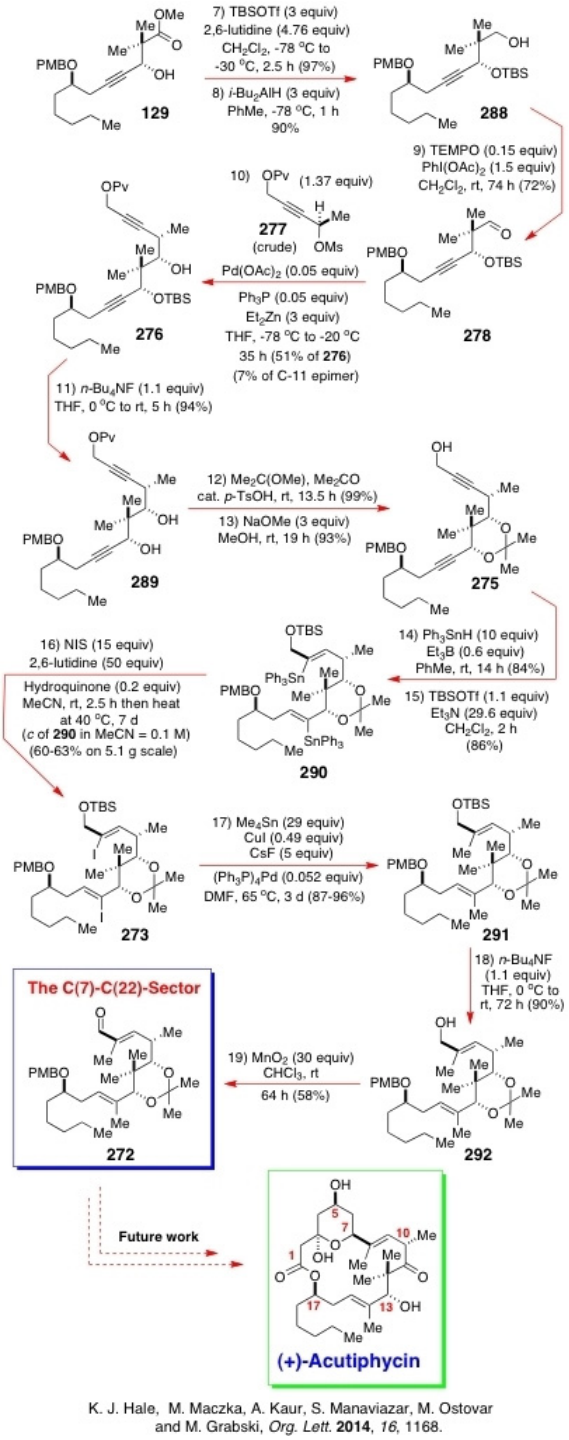
Accordingly, we followed Smith's excellent AD procedure to acquire the 1,2-diol **282** in 80–84 % ee (Scheme 45).[56a] This was then O-tosylated and the mono-O-tosylate **283** treated with NaH/Et_2O and then MeOH to generate *in situ* NaOMe, which completed formation of the epoxide **280**. Lithium acetylide-EDTA complex was then used to open **280** and alcohol **284** was protected with *p*-methoxybenzyl trichloroacetimidate. The Carreira alkynylation[52] was now best conducted under stoichiometric conditions and use of THF gave the desired product in 79–83 % yield in diastereomerically pure condition after SiO_2 flash chromatography. We have since found that *this reaction actually occurs in higher yield and performs much better when PhMe is used as the solvent*, whereupon the reaction yield increases to 88 %. The O-directed free radical hydrostannation of **129** proceeded smoothly in PhMe at rt over 7.5 h, affording the desired vinylstannane **130** as a single product, as far as we can tell, in 84 % yield. The subsequent I–Sn-exchange also proceeded smoothly with 5 equiv. of NIS at rt, but in this more hindered system than the one previously dealt with in (−)-inthomycin C, the reaction took a longer time (30 h at rt for **130**, as opposed to 4 h for **254**, Scheme 42), and the resulting vinyl iodide **285** was isolated in 84 % yield (Scheme 45).

Given that we might need to continue with this route in the future, we decided to protect **285** and investigate whether the extremely hindered vinyl iodide **286** would undergo sp3–sp2 Stille cross coupling under our newly identified Baldwin-Lee CuI/CsF promoted conditions.[50] The reaction did occur very cleanly but very slowly over 15 days at 60 °C. Because Me_4Sn boils at 76 °C, we took great care to conduct the reaction in a sealed tube at 60 °C, and because the product **287** has an identical TLC mobility to the starting vinyl iodide **286**, it proved necessary to follow it carefully by multi-elution TLC, and to stain the plates in anisaldehyde/H_2SO_4 stain, whereupon one could readily see that the product **287** stained with a different colour. This has to be one of the most challenging Stille reactions ever performed in the history of chemistry, and its success is directly attributable to the excellence and power of the Baldwin-Lee method,[50] which, in our view, is just outstanding.



Scheme 45. Our model study of the O-directed free radical hydrostannation needed to access the southern region of (+)-acutiphycin.[31]

Suitably encouraged by these breakthroughs, we began our thrust towards **272** (Scheme 46) by O-silylating the alcohol in **129**; the ester group of this product was then reduced with DIBAL-H to obtain alcohol **288** which was readily oxidized to the aldehyde **278** under Piancatelli conditions. The Marshall allenylzinc chemistry[57] with **278** thereafter gave a 51% yield of the desired adduct **276** alongside a 7% yield of the epimeric C(11)-alcohol epimer which was separated following SiO_2 flash chromatography. The TBS-ether was next cleaved from **276** with TBAF/THF, and the resulting 1,3-diol **289** re-protected as an O-isopropylidene acetal and the O-pivaloate detached.



K. J. Hale, M. Maczka, A. Kaur, S. Manaviazar, M. Ostovar and M. Grabski, *Org. Lett.* **2014**, *16*, 1168.

Scheme 46. Our double O-directed alkyl-acetylene free radical hydrostannation route to the C(7)-C(22)-sector of (+)-acutiphycin.[31]

The requisite double O-directed free radical hydrostannation on **275** proceeded beautifully and yielded primarily the bis-vinylstannane product **274** alongside small amounts of other vinylstannanes. Due to the existence of a complex rotameric/conformational equilibrium in the NMR spectrum of **274** and its O-silylation product **290**, this made precise diastereoselectivity evaluation difficult.

While, initially, we did struggle significantly to achieve the desired I–Sn exchange reaction[58] on **290**, obtaining only a 30–40% yield of **273**, after 48 h of reaction at rt, following further optimisation, we subsequently discovered a set of conditions (shown in Scheme 46) that have allowed a greatly improved 60–63% overall yield of **273** to frequently be obtained for this step on >5 g scale. Essentially, this corresponds to these two I–Sn-exchange reaction steps proceeding in *ca.* 78–80% yield.

We attained this great success under the auspices of Leverhulme Trust Grant RPG-2015-438 by: 1) performing the reaction at 40 °C for 7 days, as opposed to rt for 2 days; 2) having a significant excess of the 2,6-lutidine (50 equiv) present; 3) including 0.2 equiv. of hydroquinone in the reaction mixture, as a free radical scavenger; 4) performing the reaction in darkness; and 5) conducting the reaction with 15 equiv. of NIS.[58]

This significant lengthening of the overall reaction time, and conducting the reaction at 40 °C in MeCN,[58] proved absolutely critical to gaining this final 78–80% reaction yield per I–Sn cleavage step (which is what we typically observe in most I–Sn exchanges in less hindered systems; see Scheme 38 for a typical example). Importantly, as well, the aforementioned high yielding double I–Sn exchange reaction has now been successfully reproduced, and even conducted on 5.1 g scale.

We thus recommend that future workers who use our Ph_3SnH/cat. Et_3B/O_2 O-directed hydrostannation method should take note of this key set of observations when attempting I–Sn exchanges in *ultra-hindered* vinyl triphenylstannane systems.

Equally important as surmounting this highly challenging double I–Sn exchange hurdle was achieving a good yield in the double Stille coupling that needed to be implemented in this bis-vinyl iodide system. Once more, the Baldwin-Lee[50] variant of the Stille reaction fitted the bill perfectly on **273**,

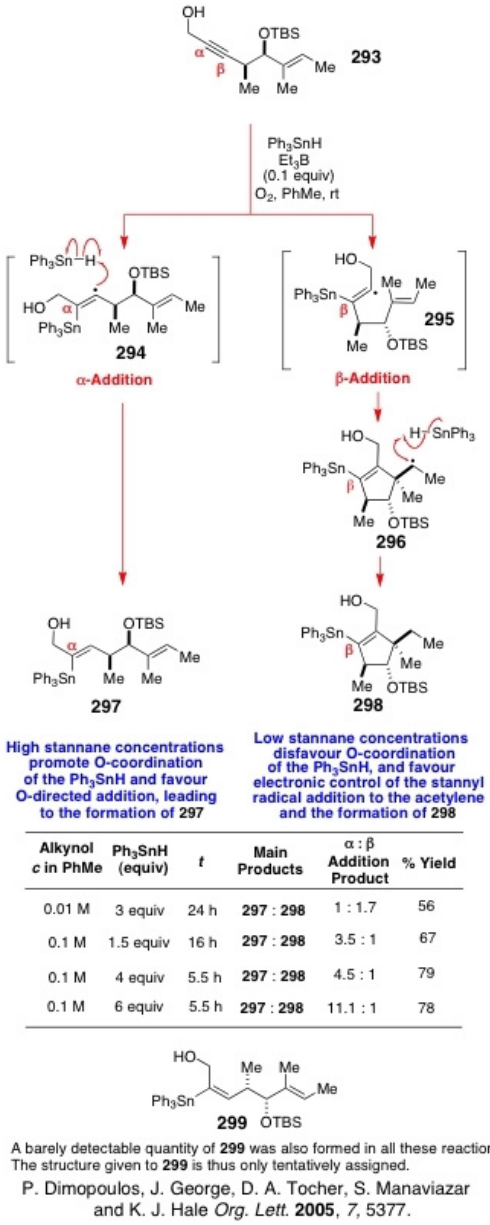
achieving a very successful two-directional coupling in a noteworthy 83 % yield once again.

In order to arrive at an advanced intermediate that has every prospect of being convertible into (+)-acutiphycin, in the near future, we duly O-desilylated **291** with TBAF and oxidized the resulting alcohol **292** with MnO_2 to obtain **272**, so completing what is now a very good route to the C(7)-C(22)-sector of (+)-acutiphycin.

We have thus powerfully demonstrated that it is possible to effect higher-order O-directed free radical hydrostannations on alkyl acetylene systems that contain multiple propargyloxy groupings, for the very first time. We have also successfully defined *high yielding* reaction conditions that efficiently effect multiple, concurrent, I–Sn exchange reactions even in highly hindered vinyl triphenylstannane systems, and we have further shown that extremely efficient *double* Stille cross couplings can be achieved with the hindered vinyl iodide products that result, particularly if one relies upon the excellent Baldwin-Lee tactics to complete the final alkene elaboration.

5. Our 2005 Experimental Investigations into the Mechanism of the O-Directed Free Radical Hydrostannation with Ph_3SnH/cat. Et_3B/O_2 in PhMe, and Our Refutal of the Later 2013 Stannylvinyl Cation Mechanistic Proposal for Dialkyl Acetylene Hydrostannation

In order to gain insights into the mechanistic origins of the high α-regiocontrol observed in these propargylically-oxygenated alkyl acetylene hydrostannation reactions with Ph_3SnH/cat. Et_3B/O_2 in PhMe at rt, in 2005, we decided to study the reaction outcome with the carefully designed probe molecule **293** at different stannane concentrations (Scheme 47).[29] We postulated that such a probe might provide useful information about the extent of α- and β-stannyl radical addition that was occurring in these reactions, under different circumstances, since the intermediary α-stannylvinyl radical **294** would show little tendency to cyclise, due to it being a thermodynamically disfavoured 4-*exo-trig* cyclisation. The latter cyclisation would, of course, produce a cyclobutylethyl type secondary radical, if it occurred, and this would be expected to spontaneously ring-open due to severe ring strain. Given this tendency, we reasoned that **294** would preferentially be trapped out as **297**, while its β-stannylvinyl radical counterpart **295** would cyclise rapidly and irreversibly to **296** (under conditions of high-dilution and low stannane concentration) due to this 5-*exo-trig* ring-closure now being much more stereoelectronically favourable. The latter radical would then H-atom abstract to give **298**.



Alkynol c in PhMe	Ph_3SnH (equiv)	t	Main Products	α : β Addition Product	% Yield
0.01 M	3 equiv	24 h	**297** : **298**	1 : 1.7	56
0.1 M	1.5 equiv	16 h	**297** : **298**	3.5 : 1	67
0.1 M	4 equiv	5.5 h	**297** : **298**	4.5 : 1	79
0.1 M	6 equiv	5.5 h	**297** : **298**	11.1 : 1	78

Scheme 47. Our study of the regiochemistry of free radical hydrostannation of probe molecule **293** with Ph_3SnH/cat. Et_3B/O_2 in PhMe at rt as a function of substrate and stannane concentration.[29] This study definitively showed that these reactions *must be O-directed* at higher stannane concentrations, since if they were exclusively under electronic control, the ratio of **297**:**298** would never change or vary. These findings thus refute the later claim of reference [35] that propargylic O-direction of the stannane is not occurring in these reactions.

At the very outset of this study, we reasoned that high stannane concentrations relative to **293** would most likely favour significant coordination of the Ph_3SnH to the propargylic-O-atom, and promote subsequent O-coordinated stannyl radical formation and "internal" Sn radical addition

to the α-acetylenic carbon of **293** to give primarily the α-O-directed hydrostannation product **297** as the favoured product following H-atom abstraction.

By way of contrast, we expected that low effective stannane concentrations relative to **293** would reduce the level of O–complexation to the stannane, and promote the intermolecular addition of isolated triphenylstannyl radicals to both acetylenic carbons, with the result that α:β-selectivity would be determined primarily by the collision frequency and the alkyne ground state polarity, rather than through any O-directed stannyl radical O-coordination/addition event. Effectively, under such circumstances, we envisioned that free radical hydrostannation would proceed primarily under electronic control.

In the end, it transpired that when we actually examined the hydrostannation of **293** at quite low effective stannane concentration, the β-product **298** predominated, but only very marginally, to the tune of 1.7:1 (Scheme 47 entry 1).[29]

Clearly, under such circumstances, stannane complexation to the propargyloxy group, and subsequent stannyl radical addition, were not occurring at a faster rate than uncoordinated triphenylstannyl radical addition to either acetylenic carbon atom, and we had apparently identified a reaction scenario where the collision energy/collision frequency, and the alkyne ground state polarity, and thus electronic control, were the primary determinants of the observed reaction outcome.

Moreover, if alkyne ground state polarity and electronic control were *always* dictating the regiochemical outcome of stannyl radical additions to propargylically-oxygenated alkyl acetylenes under our Ph_3SnH/cat. Et_3B/O_2 conditions, as is implicit in Organ and coworkers[60,35] and Curran and McFadden's[59] recent mechanistic suggestions, then one would not expect to see any significant deviation from the above β:α ratio of addition products as the stannane concentration substantially increased. Instead, the β:α addition product ratio of **298** and **297** would remain constant at around about 1.7:1 from run to run, since the reaction would continue to remain exclusively under electronic control.

However, a constancy of regiochemical outcome was not what was observed when **293** was hydrostannated at substantially higher effective Ph_3SnH concentration.[29] Instead, at higher effective stannane concentration (6 equiv), and a 0.1 M concentration of substrate in PhMe, the ratio of the β:α regioisomeric addition products **298:297** changed in a most dramatic way, moving from 1.7:1 β:α to 11.1:1 α:β (Scheme 47, entry 4).[29]

This outcome very clearly showed that alkyne ground state polarity and electronic control could not be the primary determinants of the observed product regiochemistry in the reactions of typical propargylically-oxygenated alkyl acetylenes, when the –OR group is an OH, and the same is likely true when the –OR group is an OAlkyl or $OSiR_3$ group.

Clearly, this observed regiochemical change can only be satisfactorily explained and accounted for by invoking a substantive stannane O-coordinative effect starting to dominate the outcome of the reactions that are being run at higher stannane concentrations which, in turn, translates into a marked preference for internal delivery of the resulting O-coordinated triphenylstannyl radical to the α-position of the alkyl acetylene; a fact now confirmed computationally by Alabugin et al.[71]

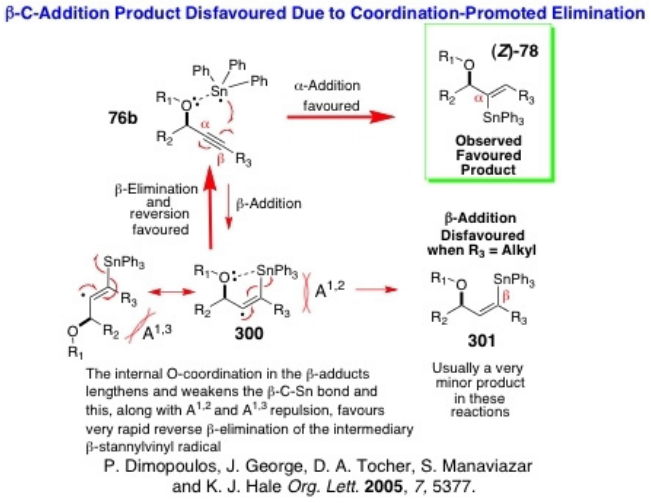
So, to summarise, these probe experiments with **293** have revealed that only a *minor* alkyne polarity effect is contributing to the outcome of free radical hydrostannations with propargylically-oxygenated alkyl acetylenes, and *this only starts to become important at low effective Ph_3SnH concentrations.* At much higher effective stannane concentrations, our studies very clearly show that the stannane must indeed be coordinating significantly to the propargylic oxygen, and this effect must be directing the observed predominant regiochemical course of these reactions.[29] *There is no other satisfactory explanation for the change in regiochemistry at higher stannane concentrations in such systems, certainly not one that is based upon alkyne ground state polarity or electronic control arguments.* Moreover, given that our 2005 mechanistic results were actually gathered on typical propargylically-oxygenated alkyl acetylenes, we believe that our proposals accurately reflect the genuine status of how these hydrostannations are proceeding in all such systems, certainly in terms of the observed α-regiochemical outcome. We will return to this point later when we reinterpret and rationalise the outcomes of the electronically extreme trifluoromethyl acetylenic alcohol systems examined by Organ,[60] Kobayashi[61] and Konno,[62] which are not at all typical, nor representative of the norm in propargylically-oxygenated alkyl acetylene systems.

Another key mechanistic insight that emerged from our studies on the probe **293** concerned the stability of the β-stannylvinyl radicals that are being generated in propargylically-oxygenated alkyl acetylene O-directed free radical hydrostannation reactions. The very fact that the β-addition/tandem vinyl radical cyclisation product **298** could easily be trapped out and detected in the reactions that were conducted at low substrate and stannane concentration, provided the first solid evidence needed to demonstrate how the intermediary β-alkyl-β-stannylvinyl radicals must typically be inherently unstable and rapidly eliminate under normal O-directed free radical hydrostannation conditions, since β-addition products are generally only seldom observed as very minor reaction constituents in our hydrostannation reactions.

We suggest that this inherent instability of β-alkyl-β-triphenylstannylvinyl radical intermediates of structure **300** is

reflective of the significant combined $A^{1,2}/A^{1,3}$-strain that they experience in various rotamers and invertomers that are being generated, a strain that will only be further exacerbated by strong internal O–Sn coordination continuing after the O-atom has directed the Sn radical to the β-position (Scheme 48). The latter interaction will also likely cause the vinyl radical C–Sn bonds in **300** to elongate and weaken significantly in an already unstable, strained, and highly reactive type of intermediate. Such bond weakening will, of course, facilitate reversion back into the starting propargyloxystannyl radical **76b**, unless **300** can be stabilised in some way, or alternatively, internally trapped, as happened with **295**.

Although radical **76b** could intramolecularly cyclise to give the β-stannyl-β-alkyl-vinyl radical **300** once more, this radical would be inherently unstable and have a very strong proclivity to revert back to **76b** due to its instability, ensuring that the only significant pathway to product is the one where α-addition occurs, since the resulting α-triphenylstannyl-β-alkyl-vinyl radicals of structure **77** (Scheme 12) cannot usually engage in strong internal O-coordination after the stannyl radical addition has occurred, and if that radical primarily populates the (*Z*)-invertomer, it can avoid destabilising $A^{1,3}$-strain and benefit from strong hyperconjugative stabilisation; it should thus have sufficiently enhanced stability and longevity to allow it to undergo fast H-atom abstraction from the Ph_3SnH or its O-coordinated counterpart via the least hindered and lower energy transition state, to give the observed β-alkyl-α-triphenylstannylalkene product **(*Z*)-78** as the predominant isomer (Scheme 12), in full accord with tenets of the Curtin-Hammett Principle.



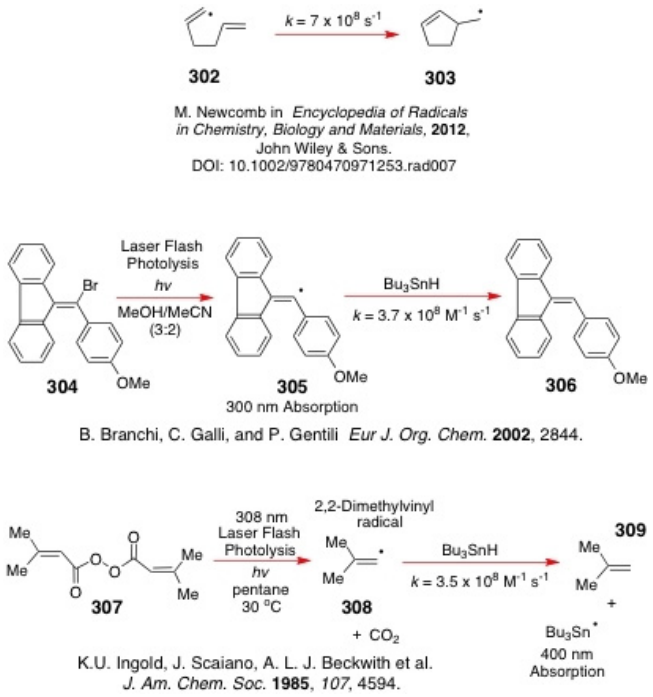
Scheme 48. A rational explanation of why the regioisomeric β-stannylvinyl radical adducts **300** readily eliminate back to **76b**, and the products **301** emerge as only minor reaction components.[29]

Such internal O-coordinative C–Sn bond lengthening and the accompanying substantial weakening of apical C–Sn bonds in β-vinyl triphenylstannane adducts has previously been documented for **71** and related structures (see Scheme 10) by Willem and Geilen, using X-ray crystallography, and this explanation was invoked by them to account for why these substrates preferentially undergo aryl-Sn cleavage, as opposed to vinyltin cleavage, when such molecules are exposed to halogens.

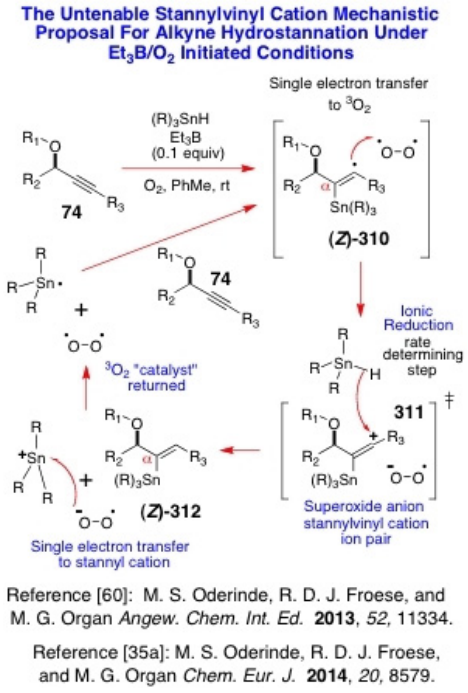
Given these past observations of Willem and Geilen,[17,18] we believe that it is entirely reasonable therefore to invoke the possibility of similar strong internal coordination occurring in β-alkyl-β-triphenylstannylvinyl radicals **300**, except now, we believe that the added presence of the β-alkyl destabilises such vinylic radicals by $A^{1,2}$ strain, unlike the situation where just a H-atom is present at the β-carbon, as is the case in the Willem/Geilen terminal alkyne systems of Scheme 10. However, despite the likely strong O-coordinative β-directing influence of the original propargylic oxygen (see Schemes 1 and 10 for examples of such behaviour), and the subsequent coordinative C–Sn bond destabilisation that would result, it is likely that it is the *collectively* magnified $A^{1,2}$ and $A^{1,3}$ repulsions that arise when an alkyl and Ph_3Sn groups are both present on the same vinylic carbon in a rapidly inverting vinylic radical that causes the vast majority of triphenylstannylvinyl radicals of β-addition to rapidly dissociate back into the starting radical **76b** before they can undergo H-atom abstraction from the stannane.

The fact also that the X-ray crystallographic plots of all the α-addition hydrostannation products shown in Figure 2[29] have revealed that there is most definitely *no* intramolecular interaction between the Ph_3Sn-substituents and the adjacent allylic O-atoms in all of these products, suggests that their intermediary bent (Z)-α-stannylvinyl radical precursors **77** (which have similar structures) will almost certainly lack this destabilising coordinative interaction as well, which logically explains why the α-stannylvinyl radicals eventually predominate, and then go on to rapidly H-atom abstract to afford the observed α-addition (*Z*)-products **(*Z*)-78** (Scheme 12). Yet again, the preferred, most stable, and most populated invertomer will likely be **(*Z*)-77** due to this invertomer not suffering from the severe $A^{1,3}$-strain that its isomeric (*E*)-radical counterpart will encounter. The pathway for H-atom abstraction from the stannane by the (*Z*)-radical **(*Z*)-77** will also usually be less sterically hindered.

If we return now to the matter of β-triphenylstannyl-β-alkyl-vinyl radical stability, and one accepts that the estimated rate constant for a vinyl radical cyclisation of the type shown in Scheme 49 is about $7 \times 10^8\ s^{-1}$ at 25 °C,[63] and the Galli,[64] Beckwith, Ingold and Scaiano[65] measured rate constants for H-atom abstraction from Bu_3SnH by the vinyl radicals **305** and **308** are between $3.5–3.7 \times 10^8\ M^{-1}\ s^{-1}$, one



Scheme 49. Experimentally determined vales of the rate constant for the vinyl radical processes depicted: cyclisation and H-atom abstraction.[63,64,65]



Scheme 50. The untenable, experimentally unsupported non-O-directed stannylvinyl cation mechanistic proposal[60,35,37,66] for explaining how **(*Z*)-312** arises from the hydrostannation of **74** with various stannanes under the $(R)_3SnH$/cat. Et_3B/O_2 conditions in PhMe. It postulates that $^3O_2$ functions as a catalytic electron carrier, initially capturing an electron from the SOMO of the α-stannylvinyl radical **(*Z*)-310** to give the α-stannylvinyl cation **311**. Although never specified by the above workers, this postulated cation is presumably associated with a liberated superoxide ion, in a solvated contact ion pair. The Scheme 50 proposers[60,35a] then suggest that their α-stannylvinyl cation intermediate **311** preferentially undergoes stereoselective ionic reduction with the excess tin hydride that is present in the reaction medium to give **(*Z*)-312**, rather than reacting with the seemingly more nucleophilic superoxide ion. No satisfactory explanation is given as to why only the (*Z*)-isomer **312** emerges. It is also postulated that the liberated superoxide anion subsequently engages in a single electron transfer (SET) to the newly liberated trialkyl-/triaryl-stannyl cation that is created, to regenerate $^3O_2$ and a new triaikyl- or triaryl-tin radical, which then propagates the radical chain reaction until all of the starting **74** is consumed. We will discuss the numerous problems that exist with this mechanistic proposal in the text, but we have to state here most unambiguously that it is fundamentally flawed.

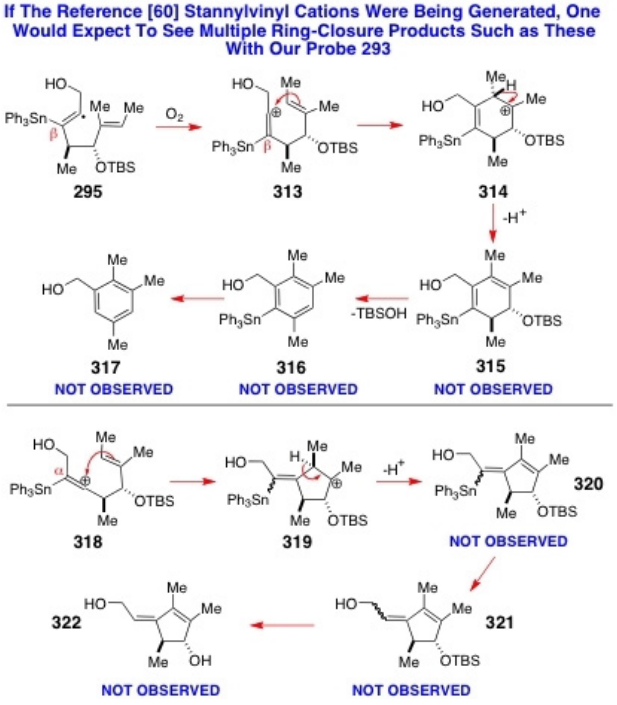
can, in turn, estimate that the rate constant for the alkyl β-triphenylstannyl-β-alkyl-vinyl radical reversal process of **300** into **76b** must therefore lie somewhere between the upper and lower limits of the above two figures. Given that Ph_3SnH is known to be much more susceptible to H-atom abstraction by carbon centred radicals than is Bu_3SnH, this means that the rate of retro-elimination of the β-triphenylstannyl addition products must be extremely fast at 25 °C.

If we now revisit the issue of product distribution in the free radical hydrostannation of **293** under conditions of low stannane concentration (Scheme 47), the very fact that the *5-exo-trig* cyclisation product **298** was the only cyclisation product that was observed in this study very strongly indicates that our O-directed hydrostannation process with Ph_3SnH/cat. Et_3B/O_2 must be totally free radical in its nature and that it cannot have any cationic component to it whatsoever, which is in total conflict with what was proposed later by Organ et al[60,66,35a,37] in 2013 (Scheme 50).

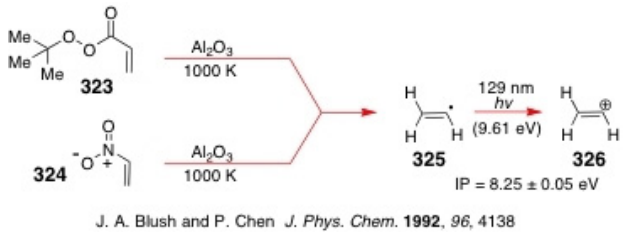
We mention this here specifically because our 2005 experimental results strongly controvert the recent mechanistic proposal of Organ and coworkers shown in Scheme 50[60,66,35a,37] who, without any genuinely supportive experimental evidence, advanced the claim that the initially formed α-trialkyl- and α-triaryl-stannyl-β-alkyl-vinyl radicals in O-directed free radical hydrostannation reactions subsequently engage in a single electron transfer (SET) process with triplet O_2, to generate an α-stannylvinyl cation and superoxide anion. Such α-stannylvinyl cations are then suggested to undergo ionic reduction with the excess stannane that is present in the solution to give the observed vinyl-stannane α-addition products and a trialkyl- or triaryl-stannyl cation, which itself is reduced by a second reverse single electron transfer (SET) from the liberated superoxide ion, to fashion a new tin radical which further propagates the radical chain. In essence, the aforementioned proposal[60,66,35a,37] has triplet oxygen behaving as a catalytic electron carrier that never gets destroyed. We have to say here and now that we, and many others in the field, fundamentally disagree with this reaction mechanism, due to it being fundamentally

flawed and incompatible with how free radicals normally react with O_2. We will now set out below the numerous objections that we have to this stannylvinyl cation mechanistic scheme, all of which render it untenable and problematical.

First, we have characterised all of the products from our O-directed hydrostannation of **293** (Scheme 47) and none of these correspond to any of those shown in Scheme 51. If the aforementioned reaction had proceeded by way of a stannylvinyl cation,[60,66,35a,37] then quite clearly we would have expected to see products such as **316** and **317** amongst the many products that would likely arise, not just **297**, **298** and **299**, which were each identified and characterised and are fully consistent with a purely free radical mechanism. The very fact that neither **320** nor **321**, nor the products of allene hydrostannation, were observed amongst the various products of hydrostannation with this probe, very strongly argues against the stannylvinyl cation mechanistic proposal of the Scheme 50 team,[60,66,35a,37] which completely disregards our own earlier 2005 mechanistic work,[29] which demonstrated that this process had to be purely free radical.



Scheme 51. Some of the multitude of products that would be expected to arise from probe **293**, if it had reacted via the stannylvinyl cation mechanism of reference [60]. However, none of these products were observed, nor allenes, nor the products of allene hydrostannation, confirming that such a cationic mechanism is not operating.



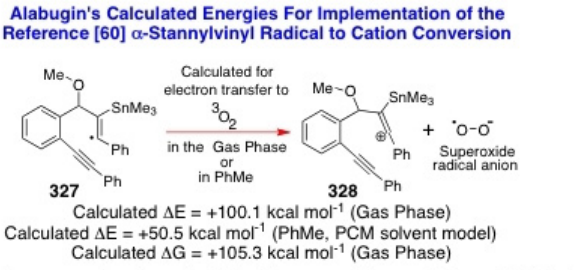
Scheme 52. Blush and Chen's experimental determination of the ionisation potential (IP) of a vinyl radical as determined by photoionisation mass spectrometry. Tremendous energy input (190.25 kcal mol^{-1}/8.25 eV) is required to bring about this ionisation.[70]

Additionally, according to Harrison and Lossing[67] the gas phase ionisation potential for a vinyl radical is 9.45 eV, as determined by mass spectrometry, which means that an energy input of approximately 218 kcal mol^{-1} would be required to bring about such a conversion in that specific system. A later Lossing IP determination[68] that used an electron beam on the vinyl radical that they had obtained from the pyrolysis of divinylsulfone yielded a lower value of 8.95 eV, as did a study by Berkowitz[69] (IP = 8.43 eV). These lower values are much more in keeping with the later vacuum-UV photoelectron spectroscopic determination of the IP of the vinyl radical by Chen and Blush,[70] which used a supersonic molecular beam and revealed that the IP was actually even lower 8.25 eV (190.25 kcal mol^{-1}) (Scheme 52).

Nevertheless, the Chen determination[70] for the energy input needed to bring about vinyl cation formation from a vinyl radical is still extraordinarily high. Consequentially, a very high ionisation potential could almost certainly be expected for the α-stannylvinyl radical to α-stannylvinyl cation transition put forward by the proposers of Scheme 50.[60,66,35a,37]

Now even if one takes into account any possible beneficial charge stabilising effects that could potentially arise from solvation and concurrent hyperconjugation with the α-tin group in a β-alkyl-α-stannylvinyl cationic system, still, the energy of formation of such a carbenium ion would be prohibitively high; far too high to allow such an entity to be formed in non-polar PhMe at room temperature through the action of catalytic $^3O_2$. The latter are the reaction conditions that are always used to perform our O-directed alkyl acetylene free radical hydrostannations with Ph_3SnH and cat. Et_3B/O_2.

Moreover, with respect to this O_2-mediated α-stannylvinyl radical to α-stannylvinyl cation transition, Alabugin and coworkers[71] have recently carried out Gaussian 09 theoretical calculations on a relevant O-directed free radical hydrostannation reaction system that proceeds through intermediates suggested to arise by the proposers of Scheme 50,[60,66,35a,37] using the β-aryl-α-trimethylstannylvinyl radical **327** as their calculation substrate (see Scheme 53). In



Scheme 53. Alabugin and coworkers' Gaussian 09 UM06-2X/LanL2Dz Basis set (for Sn) calculated energies for the molecular oxygen ($^3O_2$) mediated conversion of allylically oxygenated α-stannylvinyl radical **327** into the α-stannylvinyl cation **328** in both the gas phase and in PhMe (derived using the PCM solvent continuum model for PhMe).[71] The high energy inputs involved in both cases show that the stannylvinyl cation alkyne hydrostannation proposal[60,66,35a,37] of Scheme 50 is just not feasible.

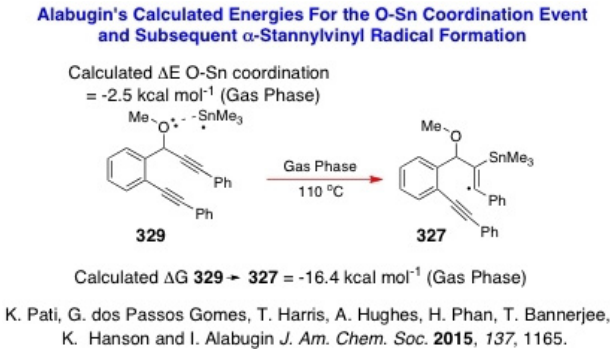
the Alabugin system[71] the initial β-aryl-α-stannylvinyl radical **327** and the subsequent stannylvinyl cation **328** were both able to benefit from additional stabilising radical and cation delocalisation into the benzene ring system. Significantly, even for this positively weighted system, the Alabugin team concluded[71] that the energy input required for conversion of the α-stannylvinyl radical **327** into the α-stannylvinyl cation **328** by $^3O_2$[60,66,35,37] would be prohibitive in the gas phase, and of the order of $+100.1$ kcal mol^{-1}, so supporting our original 2005 experimentally backed contention[29] that these O-directed free radical hydrostannations with Ph_3SnH/cat. Et_3B/O_2 are purely free radical in their nature.

Significantly, as well, Alabugin et al[71] did the same calculation after taking into account the possible beneficial effects of solvation, using single point energies derived from the polarisable continuum model (PCM) for PhMe. When they did this, the triplet oxygen mediated conversion of the α-stannylvinyl radical **327** into the corresponding α-stannylvinyl cation **328** was still prohibitively high, it now requiring an energy input of $+50.5$ kcal mol^{-1}.[71] On the basis of these new DFT calculations, and the O-directed radical cyclisation products that they independently obtained, Alabugin et al concluded that α-stannylvinyl cations[60,66,35a,37] could not be genuine intermediates in the O-directed alkyne free radical hydrostannation reaction,[23,29,32] so refuting the 2013 conclusions and calculations of the proposers of the Scheme 50 ionic pathway.[60,66,35,37]

Moreover, even the Scheme 50 team's own DFT calculations[60] produced a figure of $+47.3$ kcal mol^{-1} (2.05 eV) of energy input needed to bring about the O_2-mediated electron transfer event involving their linear α-trimethylstannyl vinyl radical transiting into the linear shaped α-trimethylstannyl vinyl cation in C_6H_6 (see Scheme 69 later on in this manuscript), which likewise would make this process impossible to achieve at rt in that solvent. The very fact, however, that this team[36] were able to successfully effect the free radical hydrostannation of alkyne **159** at room temperature with Ph_3SnH, cat. Et_3B and O_2 in C_6H_6 to give **160** as a single product in a stated 98% yield (Scheme 25) should thus have alerted them as to the untenable nature of their mechanistic hypothesis. Additionally, and in further controversion of their own later calculations,[60] the Scheme 50 team additionally reported a like result with Bu_3SnH/cat. Et_3B on **159** in C_6H_6 at rt (see Scheme 66 later on in this manuscript).[36]

The computational calculations of Alabugin et al.[71] not only support their own experimental observations and mechanistic conclusions in this area, but also ours,[29] and those of many others who have previously concluded that alkyne free radical hydrostannation reactions proceed by way of an exclusively free radical mechanism,[72b] by virtue of the products that they have obtained, whose formation cannot credibly be explained by an α-stannylvinyl cation mechanism of the type shown in Scheme 50.

Strikingly, Alabugin's calculations[71] further confirm that in the modelled conversion of **329** into **327** (Scheme 54), the O–Sn coordination event is actually *stabilising* the Sn radical in the early stages of its addition to the datively tethered acetylene, even when the free radical hydrostannation reaction is conducted at 110 °C. Indeed, this interaction actually provides a stabilisation of about -2.5 kcal mol^{-1}. This figure would probably be even more exergonic for an O-coordinated Ph_3Sn radical due to its higher Lewis acidity and its ability to partially delocalise the Sn radical into the attached Ph ring systems, but we do recognise that ordinarily pyramidal Ph_3Sn radicals themselves primarily prefer to have the radical sitting on the tin atom, according to ESR spectroscopy.[72b] The Alagubin calculations further show that this O–Sn interaction



Scheme 54. Alabugin and coworkers' Gaussian 09 UM06-2X/LanL2Dz Basis set (for Sn) calculated energies for formation of the allylically oxygenated α-stannylvinyl radical **327** from the O-coordinated tin radical **329** in the gas phase. Note the favourable energy gain associated with O-coordination.[71]

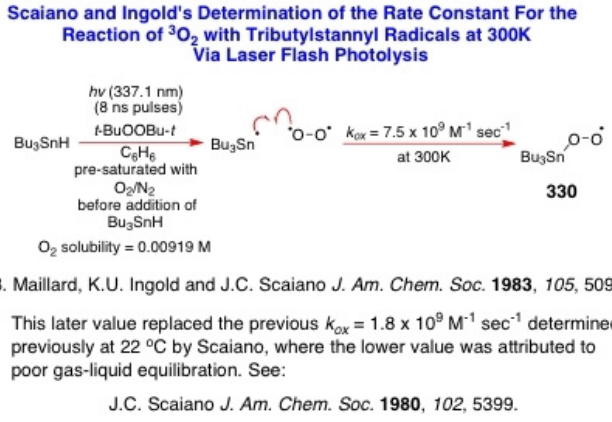
dissipates as the reaction transition state becomes more advanced and it transits into the α-trimethylstannyl-β-aryl-vinyl radical intermediate, as was first proposed by us in our 2005 paper on the O-directed alkyl-acetylene free radical hydrostannation mechanism with Ph_3SnH.[29] This latter assertion of ours followed our detailed examination of the X-ray crystal structures of the alkyl vinyl triphenylstannanes presented in Figure 2 (which show that the O–Sn interaction is not usually present in such compounds), and the hydro-stannation mechanistic studies that we ourselves[29] had performed on probe **293** (Scheme 47).

Both singularly, and collectively, the Alabugin[71] and Hale-Manaviazar[29] work on the O-directed disubstituted alkyl acetylene hydrostannation reaction mechanism very strongly opposes the recent mechanistic suggestions[60,66,35,37] including implicit ones[59] that electronic effects and ground state polarity are the primary determinants of the observed α-regiocontrol in most propargylically-oxygenated dialkyl acetylene systems; this is just not the case.

We will now move on to discuss yet another problem with the α-stannylvinyl cation mechanism of Scheme 50 for the O-directed free radical hydrostannation of alkyl- and aryl-acetylenes.[60,66,35a,37] Specifically, this centres on the incorrectly proposed role for O_2 in this reaction, which is discordant with all previous experimental observations that have been made for how trialkylstannyl- and triarylstannyl radicals react with O_2, and with how vinyl radicals also react with O_2, for which discrete products and intermediates have definitively been identified and spectroscopically characterised in multiple systems, and reaction rate constants even determined, in a great many cases. *In such reactions, specific mechanistic pathways are always followed where the radicals invariably add irreversibly to the $^3O_2$, to give peroxyradical adducts.* None of these radical additions has ever been observed to involve rapid donation of a single electron to O_2 *without* concomitant formation of a peroxy radical adduct. So, hypothetically, even if an α-stannylvinyl cation was transiently being generated in the manner that has been indicated,[60,66,35,37] not that there is any evidence to suggest that this is the case, the distance over which such an electron transfer would have to take place would have to be so small, and the resulting cation-superoxide anion contact ion pair so reactive, that the two partners would have to immediately come together to form the observed peroxy radical adducts.

Moreover, in the mechanistic pathway proposed in Scheme 50, the propounders,[60,66,35a,37] contend that O_2 acts purely as a reversible *catalytic* electron carrier in alkyl- and aryl-acetylene hydrostannation reactions mediated by $R_3SnH/Et_3B/O_2$, and that Bu_3Sn radicals happily coexist alongside O_2. Yet, their proposal is countered by many prior literature reports which have all carefully defined how O_2 reacts with both $(R)_3Sn^{\cdot}$ and vinyl radicals, to show its obvious error. In the latter regard, the vulnerabilities of the Scheme 50 mechanistic proposal[60,66,35a,37] will now be discussed in more detail below.

First, in 1983, Scaiano and Ingold[73] jointly showed (Scheme 55) that $Bu_3Sn^{\cdot}$ radicals react rapidly with O_2 to give $Bu_3SnO–O$ radicals **330** with an "unusually fast" reaction rate constant, estimated to be around $7.5 \times 10^9\ M^{-1}s^{-1}$ in benzene, as determined by laser flash photolysis.



Scheme 55. Scaiano and Ingold's determination of the rate constant for the reaction of O_2 with tributylstannyl radicals as determined by laser flash photolysis. A similar reaction methodology was used on both occasions.[73]

Second, this same tributylstannylperoxy radical (g= 2.025) was unambiguously characterised by ESR spectroscopy in an O_2 saturated cyclopropane/PhMe/CF_3Cl/CF_2Cl_2 solvent mix at 153 K by Howard, Tait and Tong in 1979, it having been generated photochemically from Bu_3SnH in the presence of di-*t*-butylperoxide (as a source of *t*-$BuO^{\cdot}$).[74] Indeed, the tributyl-stannylperoxy radical so generated was found to be quite stable under these conditions as long as the temperature was kept below 193 K, and it was found to have a linewidth of 15G at 153 K (Scheme 56). These same workers also recorded and interpreted the ESR spectrum for the $Ph_3SnO–O^{\cdot}$ radical (g=2.020) obtained from the

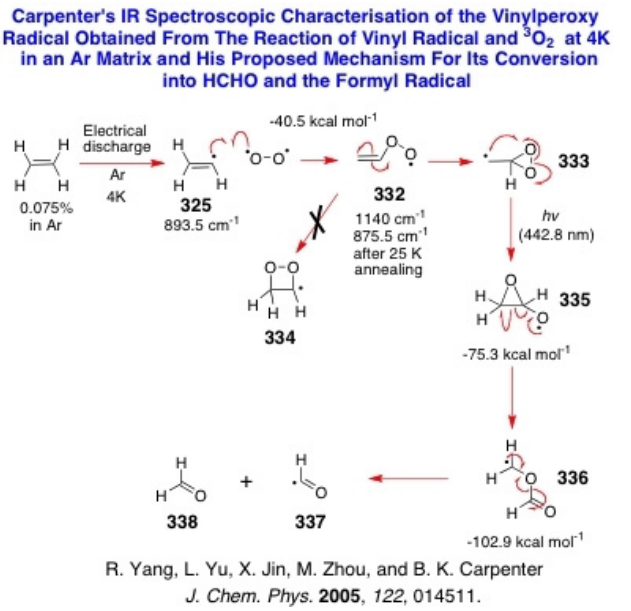
Scheme 56. Howard, Tait and Tong's ESR determination of the structures stannylperoxy radicals generated from the reaction of $^3O_2$ with $(R)_3Sn^{\cdot}$.[74]

analogous reaction between triplet O_2 and Ph_3SnH under identical circumstances. Together, this collective work definitively revealed that, once formed, $Bu_3SnO–O^{\cdot}$ and $Ph_3SnO–O^{\cdot}$ radicals show no tendency to dissociate to regenerate stoichiometric O_2 and the starter $Bu_3Sn^{\cdot}$ and $Ph_3Sn^{\cdot}$ radicals, which simply cannot coexist with O_2 in the manner indicated by the proposers of the mechanism in Scheme 50.[60,66,35a,37] Indeed, the spectroscopic data for such $R_3SnO–O^{\cdot}$ radicals **331** is structurally consistent with the existence of a reversible equilibrium between a cyclic three-membered stannyl peroxide, where the radical sits on Sn, and an open linear form (Scheme 56). Howard and Tait also showed that such radicals self-decay irreversibly with second-order kinetics. Clearly, the collective work of Ingold and Scaiano,[73] and Howard, Tait and Tong,[74] is at total variance with the 2013–2014 stannylvinyl cationic mechanism that has been put forward by the proposers of Scheme 50,[60,66,35,37] since R_3Sn radicals generally add to O_2 whenever they get the opportunity.

Additionally, carbon-centred free radicals $R^{\cdot}$ have long been known to react with triplet oxygen to form peroxyradical adducts $ROO^{\cdot}$, for which a great many rate constants have been accurately determined. In the specific case of vinyl radicals, they always prefer to add to triplet oxygen to form a vinylperoxy radical, rather than forming a distinct intermediary vinyl cation of the type found in Scheme 50,[60,66,35a,37] and the reaction between vinyl radical and O_2 is one that has been particularly well studied. Representative amongst these studies is the landmark work of Carpenter et al who showed that addition of the vinyl radical ($C_2H_3^{\cdot}$) to O_2 is exothermic, it exhibiting a

$$\Delta E = -40.8\,\text{kcal/mol}.$$[75]

The latter vinylperoxy radical **332** then undergoes internal 3-*exo-trig* ring-closure to give a cyclic dioxiranyl methyl radical **333** that subsequently rearranges (possibly photochemically) into formaldehyde and a formyl radical, which then breaks down into multiple products (Scheme 57). This alkene self-cleavage process is the primary reaction pathway followed by peroxyvinyl radicals at ambient temperature and pressure, and the 3-*exo-trig* mode of ring-closure is of lower activation energy than the corresponding 4-*endo-trig* cyclisation to the dioxetanyl radical **334**, which is associated with much higher steric strain. In terms of defining how vinyl radical itself reacts with triplet O_2, the work of the Carpenter team is unambiguous,[75] this group having assigned the 1140 cm^{-1} and 875.5 cm^{-1} absorptions to the vinyl peroxy radical **332** via infrared absorption spectroscopy, having generated the radical in an Argon matrix at 4 K that was subsequently annealed at 25 K.

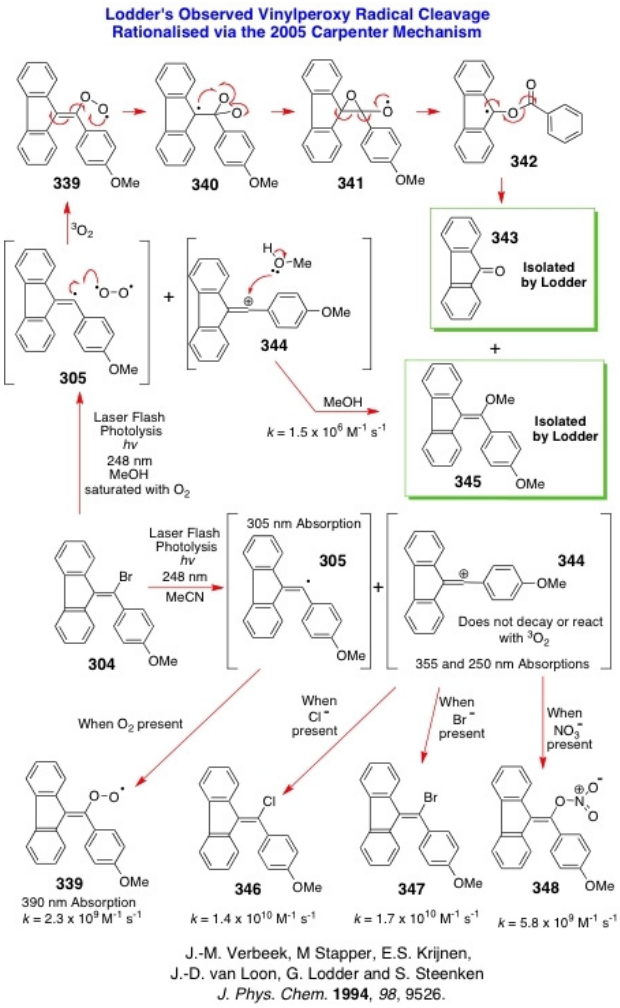


Scheme 57. Carpenter's matrix isolation IR spectroscopic and theoretical study of how vinyl radical reacts with $^3O_2$. Carpenter observed both the vinyl peroxyradical **332** and the vinyl radical **325** at the IR absorptions indicated.[75]

Moreover, using the technique of laser flash photolysis, in 1994 Lodder and coworkers[76] likewise observed that styryl type radicals $Ar_2C{=}C–Ar$ react rapidly with O_2 ($k = 2.3 \times 10^9\ M^{-1}s^{-1}$) in deoxygenated MeCN (Scheme 58). Yet again, the vinylperoxy radicals $Ar_2C{=}C(Ar)–O_2^{\cdot}$ **339** that were formed were spectroscopically characterised via their distinct and characteristic absorption band at 390 nm in their time-resolved laser light-derived UV absorption spectra.

Illustratively, Lodder et al[76] studied the photochemical formation of both the vinyl radical **305** and the vinyl cation **344** from vinyl bromide **304** in deoxygenated MeCN by laser flash photolysis at 248 nm. They noted that when the time-resolved UV absorption spectra were recorded 0.2 μs after the initial pulse, a very strong absorption band appeared at λ_{max} 355 nm, alongside a second very narrow positive band at 250 nm. Both of these absorption bands decayed at an identical rate, very rapidly over 7 μs, in a near exponential way ($k = 1.5 \times 10^5\ s^{-1}$). The Lodder team assigned these two bands to the vinyl cation **344**. Alongside these absorptions, a third much weaker absorption band was also observed at 305 nm, whose intensity did not diminish significantly even after 33 μs, a timeframe over which the 355 and 250 nm bands had long decayed and disappeared. Lodder assigned this third 305 nm band to the vinyl radical **305**.[76]

Lodder[76] found that when the same laser flash photolysis experiment was conducted in MeCN that had been pre-saturated with O_2, the 305 nm band was already absent 0.2 μs



Scheme 58. Some key representative observations made by Lodder et al[76] in their landmark 1994 laser flash photolysis study of the reactions of styryl radicals with $^3O_2$ and the corresponding styryl cations with nucleophiles. Significantly, they conclusively showed that vinyl radicals react with $^3O_2$ to give vinylperoxy radicals that then oxidatively cleave. In this instance, the fluorenone **343** was actually isolated by Lodder, proving that vinylic radicals typically undergo alkene oxidative cleavage, by a mechanism that we now know to be analogous to that proposed later in 2005 by Carpenter.[75] This work further refutes the Scheme 50 mechanistic suggestion for the role of O_2 in O-directed free radical hydrostannations of alkyl- and aryl- acetylenes, it proving that vinyl radicals react with O_2 by a totally different radical addition pathway that subsequently involves alkene cleavage.

after the initial pulse had been delivered, and was now replaced by a new weak absorption band at 390 nm which, quite reasonably, was assigned to the vinylperoxy radical **339**. Significantly, the 355 nm and 250 nm bands for the vinyl cation **344** both remained totally unaffected by the introduction of the O_2. Lodder's determination of the rate constant for the vinyl radical **305** adding to O_2 was $k = 2.3 \times 10^9\ M^{-1}\,s^{-1}$, which is extremely fast.[76]

Lodder et al[76] also recorded the laser flash photolysis spectra of **344** in deoxygenated MeCN under identical conditions to those used initially, except now in the presence of various negatively charged halide and oxyanion nucleophiles. Significantly, the pair of 250 nm and 355 nm absorption bands for the vinyl cation **344** both completely disappeared under these circumstances, due to **344** having been rapidly trapped by the added nucleophiles. Indeed, the vinyl cation **344** reacted with such rapidity that the rate constants were close to the diffusion controlled limit of $2 \times 10^{10}\ M^{-1}\,s^{-1}$. Thus, for NO_3^- ion the value of k was $5.8 \times 10^9\ M^{-1}\,s^{-1}$, while for Cl^- k was $1.4 \times 10^{10}\ M^{-1}\,s^{-1}$.

Now if the vinyl radical **305** had reacted with O_2 by the reversible electron transfer mechanism that has been incorrectly suggested to operate for (*Z*)-**310** in Scheme 50,[60,66,35,37] it would have required the vinyl cation **344** and superoxide ion to be generated as a contact ion pair, and that cation would subsequently have needed to react irreversibly with the superoxide anion to give **339** with a rate constant close to that observed for NO_3^- i.e. $k = 5.8 \times 10^9\ M^{-1}\,s^{-1}$, to account for the peroxy radical adduct **339** spectroscopically observed by Lodder at 390 nm in MeCN, and the fluorenone **343** also physically isolated and purified by Lodder.[76]

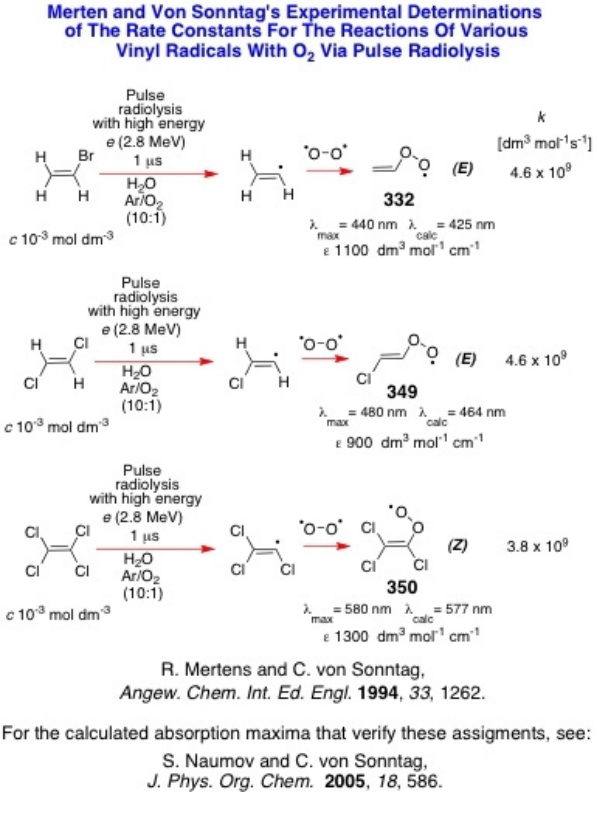
Given that an exothermic and much lower energy vinyl radical addition pathway would be available for the more direct transit of **305** into the observed vinylperoxy radical **339**, it seems most unlikely that a triplet O_2/vinyl radical union would proceed by way of such a rapid ionisation event to give the vinyl cation **344** followed by a rapid nucleophilic attack of superoxide ion, certainly not at room temperature. Such a process would be energetically unfeasible and violate the Principle of Least Nuclear Motion.[77]

On top of this, in 1994, von Sonntag and Mertens[78a] of the Max Planck Institute in Mulheim, deliberately generated a large number of vinylperoxy radicals of varying structure through the pulse radiolysis of different vinyl halides in aqueous solution that had been pre-saturated with a 10:1 Ar:O_2 gas mixture (Scheme 59).[78a] Basically, in these experiments, a short 1 μs pulse of high energy electrons (2.8 MeV) was applied to the aforementioned solutions from an ionising radiation source, at low vinyl halide substrate concentration (10^{-3} mol dm^{-3}). In these experiments, the reaction solvent, H_2O, always preferentially undergoes ionisation on a very fast timescale to produce a wide range of reactive species that includes hydrated electrons, hydroxy radicals, H-atoms, hydrogen peroxide and hydrogen gas.

Under such circumstances, the hydrated electrons react extremely rapidly with the vinyl halides that are present in the solutions to give the halovinyl radical anions, which immediately dissociate into vinyl radicals and the corresponding halide ions. The Ar gas was deliberately added to the mixtures to greatly reduce the amount of competitive

hydrated electron transfer to the O_2 which is normally a very rapid process under such conditions, and gives superoxide radical anion. "Buffering" with a large excess of Ar helped favour the hydrated electron transfer to the vinyl halide, which itself was a facile reaction. The vinyl radicals that were formed were then observed to react rapidly with the O_2 that was present in the solution to give vinylperoxy radicals whose existence was unambiguously proven by observation of the expected characteristic UV absorptions that are detailed in Scheme 59. The validity of these vinylperoxy UV absorption maxima was later confirmed in 2005 by high-level theoretical calculations conducted using the UTD/B3LYP/6-31 + (d,p) method by von Sonntag.[78b] The rate constants for the various O_2 vinyl radical trappings are shown in Scheme 59[78] and they are close to the diffusion-controlled limit, as was found by Lodder.[76]

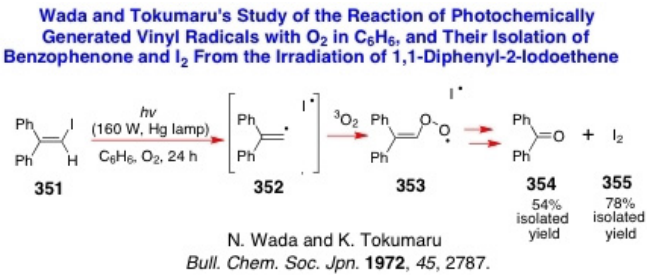
Significantly, as well, von Sonntag found these vinyl radical additions were irreversible[78] as was found to be the case by Carpenter et al,[75] a decade later. So, these combined observations would all appear to strongly counter the errant



Scheme 59. Mertens and von Sonntag's experimental determination of the rate constants for the reactions of various vinylic radicals with molecular oxygen under pulse radiolysis conditions.[78a] The assignments of the λ_{max} values were later confirmed by von Sonntag and Naumov via quantum mechanical calculations[78b] performed on the vinylperoxy radical structures **332**, **349** and **350**, attesting to their validity.

mechanistic claims of Organ, Oderinde and Froese about how vinyl radicals typically react with triplet O_2.[60,35a]

Besides these results, and predating them by more than two decades, Tokumaru and Wada had extensively studied how 1-methyl-2-phenylvinyl radicals react with O_2 in 1972, and they found that benzaldehyde was the predominant product of such reactions.[79] Additionally when they photolytically generated the vinylic radical **352** from 1,1-diphenyl-2-iodoethylene **351** by UV irradiation in C_6H_6 in the presence of a constant a stream of O_2 (Scheme 60), once more, they observed oxidative cleavage of the alkene, isolating benzophenone **354** as the major reaction product in 54% yield alongside I_2 in 78% of the theoretical yield. No other products were formed, indicating that alkene oxidative cleavage via the vinylperoxy radical is always the normal course of events for a vinyl radical oxidation with O_2, not single electron transfer with concomitant vinyl cation formation, as has been advocated by the proposers of the Scheme 50 mechanism,[60,66,35,37] and this point is absolutely critical to understanding why the alkyne hydrostannation reaction with R_3SnH/cat Et_3B/O_2 cannot possibly proceed by such a mechanism. Vinyl radicals simply do not react with O_2 in the manner suggested by these workers. Instead, they always react to form vinylperoxy radical adducts.



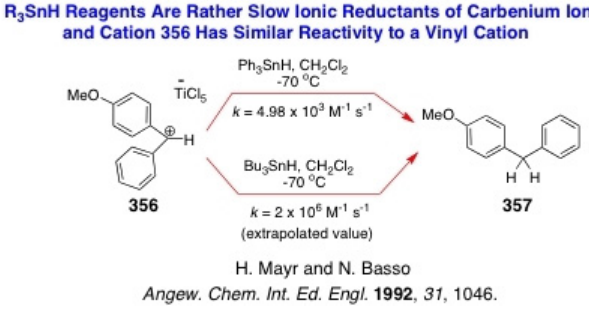
Scheme 60. Wada and Tokumaru's study[79] of how 1,1-diphenylvinyl radicals react with molecular oxygen, and how this leads to alkene cleavage to benzophenone via the Carpenter mechanism.[75]

At best, the formation of these carbonyl-containing products shows that O_2 cannot possibly accept a single electron from a vinylic radical without also concomitantly engaging the superoxide radical anion itself, and then undergoing subsequent double bond cleavage via a cyclic dioxiranyl methyl radical type mechanism. So, even if an α-stannylvinyl cation was being generated, as has been proposed by the authors of Scheme 50,[60,66,35,37] it would have to instantaneously react with the partnering superoxide ion in the contact ion pair, rather than persisting for any significant period of time to undergo a quite slow ionic reduction by the stannane. In addition, the resulting stannylvinyl peroxy radicals would also likely serve as powerful H-atom

abstractors for the R_3SnH reagent that is present in excess, in addition to engaging in internal vinylstannane oxidative cleavage reactions, which would ultimately cleave the newly fashioned alkenes via the Carpenter mechanism.[75] However, such cleavage is not observed.

With regard to the issue of ionic reduction of vinyl cation species by stannanes, of great relevance to the present discussion are the rate constants that have been measured for the reduction of $(p\text{-}MeOC_6H_4)(Ph)CH^+$ carbenium ions by stannanes, as determined by Mayr and Basso in 1992,[80] which are far slower than the rates of O_2 capture by a vinyl radical as determined by Lodder in 1994.[76]

Thus, the rate constant for hydride transfer to $(p\text{-}MeOC_6H_4)(Ph)CH^+$ from Ph_3SnH in CH_2Cl_2 at $-70\,^{\circ}C$ is $4.98 \times 10^3\,L\,mol^{-1}\,s^{-1}$, which shows that Ph_3SnH is a fairly poor ionic reductant for even a quite long lived carbenium ion (Scheme 61). Significantly, as well, Mayr has also recently commented on this type of diaryl carbocation having a similar level of reactivity towards nucleophiles as the vinyl cation **344**.[81] Such a slow rate of intermolecular hydride transfer *via an ionic mechanism* would simply not compete with the much faster rate of superoxide anion attack that would inevitably occur within an intermediary vinyl cation-superoxide contact ion pair, assuming superoxide radical anion was hypothetically being formed by single electron transfer to O_2 as is being claimed by the workers who have proposed the mechanism in Scheme 50.[60,66,35,37]

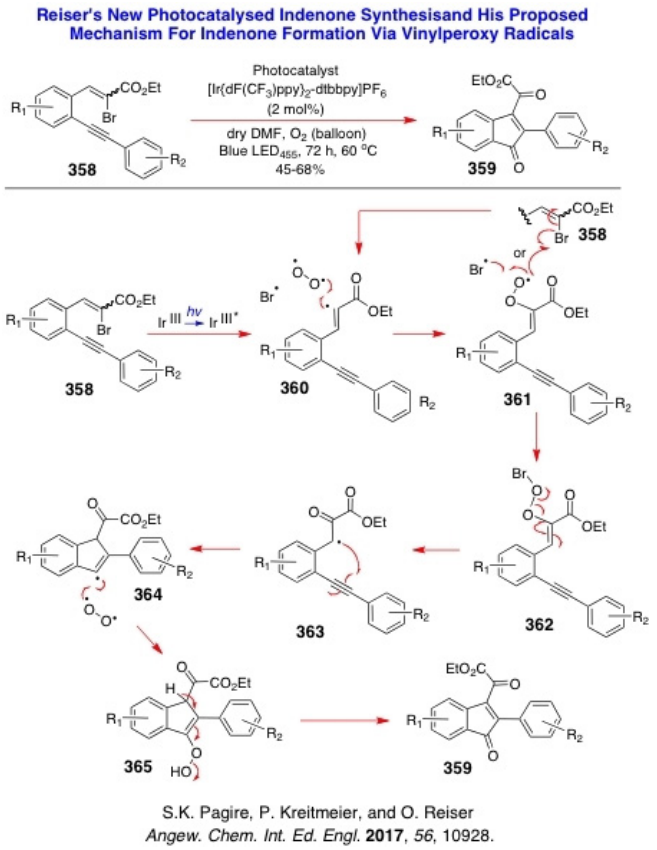


Scheme 61. Mayr and Basso have found that the ionic reduction of diaryl carbenium ions is rather slow with Ph_3SnH,[80] and such carbenium ions have similar reactivity to vinyl cations such as **344**.[81] By way of contrast, vinyl radical H-atom abstraction from Ph_3SnH is very fast ($k > 3.7 \times 10^8\,M^{-1}\,s^{-1}$). This further calls into question the validity of the stannylvinyl cation mechanism that has been outlined in Scheme 50.[60,66,35,37]

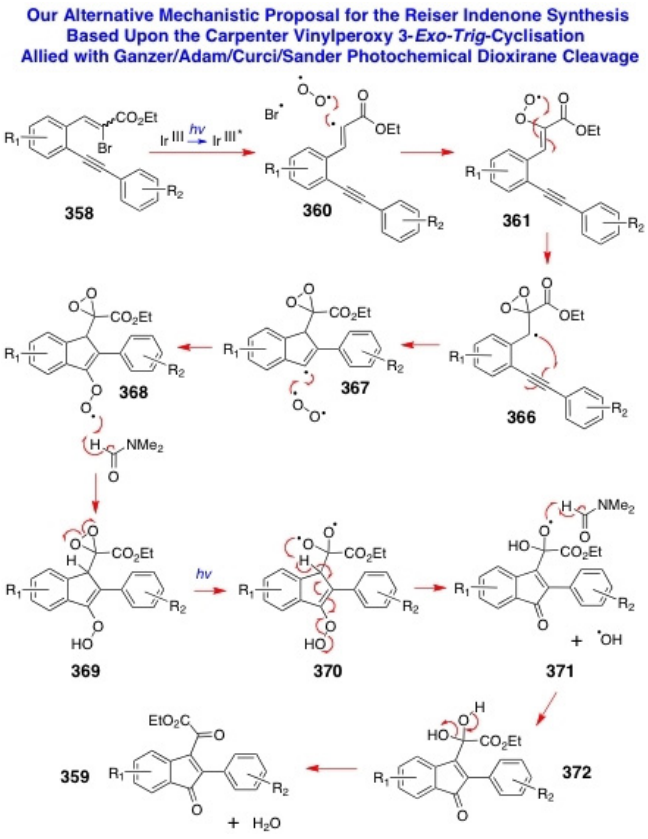
By way of contrast, the rate of free radical H-atom abstraction by an α-stannylvinyl radical from Bu_3SnH would be extremely fast and occur with a rate constant close to $k = 3.7 \times 10^8\,M^{-1}\,s^{-1}$, based on work in related systems by Galli,[64] Ingold and Scaiano.[65] So, just based upon our our knowledge of the poor hydride donating power of stannanes towards carbenium ions under ionic conditions, particularly in non-polar solvents like PhMe, one can soon appreciate why the greater majority of expert organic chemists believe that α-stannylvinyl radicals will always prefer to rapidly H-atom abstract from a stannane by a free radical mechanism, rather than reacting via an alternate, much higher energy, vinyl cation pathway that would be unnecessarily circuitous, and violate Rice and Teller's Principle of Least Nuclear Motion.[77] The latter, according to Hine, *"states that those elementary reactions will be favored that involve the least change in atomic position and electronic configuration."*[77c] due to them having a lower activation energy. Moreover the very fact that vinyl α-triphenylstannane product formation occurs, rather than vinyl peroxy radical formation with accompanying vinyl stannane cleavage, further argues very strongly against the validity of the Scheme 50 mechanism.[60,66,35,37]

However, as one final testament to how vinyl radicals react with O_2 (even supplied by a balloon), an exciting new synthesis of indenones has recently been developed by Reiser et al[82] which is based upon the formation of vinylperoxy radical intermediates from vinyl radicals at two distinct stages, in what is a most elegant radical cyclisation cascade (Scheme 62). A key underpinning element of the Reiser work is his visible-light mediated generation of the generalised vinylic radical **360** which set the stage for its subsequent addition to O_2 to give the vinylperoxy radical of general structure **361**. Reiser then invoked that **361** underwent conversion into **362** (presumably by attack of **361** on **358** or by combination with Br radical (but a reaction with **358** looks somewhat better). The latter vinylperoxy bromide **362** was then suggested to undergo radical cleavage to afford the α-keto radical **363** which thereafter attacked the tethered alkyne to form a new vinyl radical **364** that was trapped by O_2. Of course, the latter step generated a new peroxyvinyl radical which H-atom abstracted to give **365** which then set the stage for elimination of H_2O to provide the indenone **359**. A weakpoint with this mechanism, however, is its requirement for a photo-catalytically generated Br atom or **358** to combine with the photo-catalytically generated vinyl peroxyradical **361** to give the unstable **362**. Trapping with **358** would also generate more **360** and potentially dispense with the need for continuous photoirradiation (for 72 h) which is apparently a requirement for these reactions to proceed.

An alternate tentative mechanism that avoids this is shown in Scheme 63. It is more attractive, we believe, since it aligns much more closely with the now very widely accepted Carpenter mechanism[75] for how vinylperoxy radicals react when they are first generated. In this respect, the vinylperoxy radical **361** is converted into the radical **366** which undergoes the 5-*endo-dig* cyclisation into **367**. We then suggest that **367** is converted into the hydroperoxide **369** via O_2 trapping of



Scheme 62. Reiser's novel deployment of vinylperoxy radicals in a new visible-light photocatalysed synthesis of indenones; this is his proposed mechanism.[82]



Scheme 63. An alternate *tentative* mechanistic proposal for how the Reiser indenone synthesis may be proceeding. This new mechanism accommodates the known tendency of vinylperoxy radicals to undergo 3-*exo-trig* cyclisation, and the known photochemical lability of dioxiranes. It also does not require two catalytically generated radicals to find one another and react in solution, nor **361** to react with **358** to generate unstable **362** as is required in Reiser's alternative mechanism of Scheme 62.

the vinyl radical **367** and H-atom abstraction from DMF by the vinylperoxy radical **368**, a reaction known to occur with facility for alkylperoxy radicals.[83]

This alternate mechanism also invokes the occurrence of a photochemically mediated cleavage of the strained dioxirane in **369**, a reaction known to proceed with facility in dioxirane chemistry[75,84] and, which, if it did occur would give **370** to trigger an eliminative breakdown of the unstable vinyl peroxide into the hemiacetaloxy radical **371**, which would finally undergo H-atom abstraction from the solvent DMF[83] to convert into the indenone **359**.

So, once more, even this elegant 2017 work of Reiser further calls into question the veracity of the Organ team's hydrostannylative mechanistic proposal of Scheme 50,[60,66,35a,37] while also actually proving that vinyl peroxy radicals can be harnessed in genuinely synthetically useful ways, without invariably undergoing C=C double bond cleavage. However, for the latter to occur, a suitable radical trap must be present. Reiser thus took these highly reactive and fleeting reaction intermediates out of the shadows and used them to develop stunning new chemistry of great synthetic worth for the first time ever.

If we return now to the hydrostannation mechanistic discussion at hand. Since the aforementioned rate constant determinations of Lodder[76] and von Sonntag[78] have definitively shown that vinyl radical/O_2 addition occurs more rapidly than H-atom abstraction from Bu_3SnH by vinyl radicals ($k_{H\text{-atom abstraction}} = 3.7-3.5\times10^8\ M^{-1}\,s^{-1}$), and we have also now seen this data presented alongside Reiser's brilliant work,[82] we must now explain why O_2-mediated alkene cleavage products are never usually seen in free radical hydrostannations initiated by "catalytic" amounts of Et_3B.

Basically, it is because the O_2 concentration in solution is generally always extremely low in a Et_3B initiated hydrostannation that is run in PhMe under N_2 (or Ar) with an aliquot of air, and the Ph_3SnH (or Bu_3SnH) is always present in massive excess, compared with the amount of O_2 that is ever in the solution, even at reaction end. At least this is the

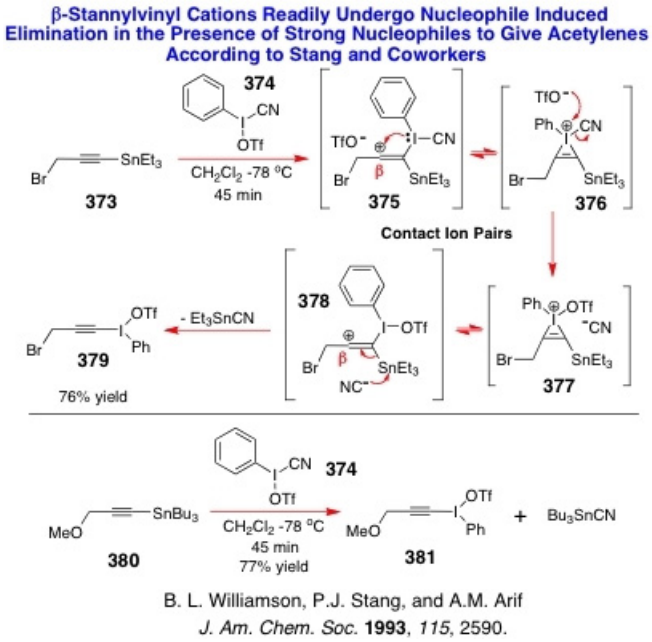
case under the conditions under which we run these reactions. Simple Collision Theory (for all of its deficiencies) thus predicts that the O_2/stannylvinyl radical collision frequency Z will actually be extremely low for a reaction that is initiated by only a miniscule amount of active radical initiator, since only a very tiny amount of the stannylvinyl radical intermediate will ever be present in the solution at any moment in time and, statistically, such a highly reactive radical will always be much more likely to encounter stannane than it will O_2 dissolved in the solution. Moreover, due to the extremely fast rate of H-atom abstraction from a stannane by a vinyl radical, the latter process will thus always win over the alternate O_2 union, particularly when the stannane is present in significant excess compared with the amount of O_2.

Indeed, all experimental observations made to date very strongly bear this out, with intermediary α-stannylvinyl radicals always preferring to H-atom abstract from the stannane to generate the observed α-vinylstannane products, rather than ever reacting with the tiny amounts of O_2 that are present in the PhMe reaction solvent to form vinyl peroxy radical adducts, and the usual so-derived carbonyl products (which are just never observed).

Likewise the electron transfer event that has been claimed to be important by the proposers of Scheme 50,[60,66,35,37] will also be non-competitive because of the low rates of encounter of the minute quantities of stannylvinyl radical constantly being generated in solution with the very small number of O_2 molecules that will be present, which will again only be tiny compared to the significant amount of stannane that will ever be present.

In addition, the amount of Et_3B initiator that will typically be present in solution at the outset will also be likely to be there in greater quantity than the intermediary α-stannylvinyl radicals that will continually be generated, and this Et_3B will likewise compete to gradually sequester most of the dissolved O_2 over time to generate $Et^{\cdot}$ and other initiating peroxy radicals, as described by Davies, Ingold, Roberts and others,[85] and these will initiate and propagate further rounds of the radical chain O-directed hydrostannation process, until all of the starting acetylene is eventually consumed by the excess stannane that is always present.

Additionally, Stang and coworkers[86] have observed that when an α-stannylvinyl cation is generated in the presence of a nucleophilic, negatively charged, counter-anion, the α-stannylvinyl cation will always undergo nucleophile-induced eliminative collapse to give the functionalised acetylene in high yield (see Scheme 64) along with the nucleophile-bound organotin. On the basis of Stang's definitive work,[86] if the α-stannylvinyl cation/superoxide anion ion pair of Scheme 50 was being formed, one would expect the highly nucleophilic superoxide anion either to: 1) react with the cation to form a stannylvinylperoxy radical that would undergo double bond oxidative cleavage via the Carpenter mechanism,[75] or 2) attack the Sn moiety to give back the parent acetylene and a stannyl peroxide.



Scheme 64. When stannylvinyl cations are generated in the presence of good nucleophiles, they typically undergo nucleophile-induced fragmentive elimination to give the acetylenes, according to Stang et al.[86] The fact that the group who have put forward the Scheme 50 mechanism have reported many ≥95% reaction yields[36] is thus incompatible with the formation of a β-stannylvinyl cation/superoxide anion contact ion pair which would almost certainly react with one another to give back either the parent acetylene or a stannylvinylperoxy radical that would then undergo oxidative cleavage. These observations once more rule out the stannylvinyl cation mechanism of Scheme 50 for dialkyl acetylene hydrostannation with R_3SnH/cat. Et_3B/O_2.

Moreover, given that a large number of the stated[36] yields for the Bu_3SnH/cat. Et_3B/O_2/PhMe procedure are >95%, with some even at the 99% level, such yields are totally irreconcilable with the stannylvinyl cation mechanism[60] of Scheme 50, given Stang's prior work,[86] since any intermediary stannylvinyl cation would inevitably react much more slowly with neutral Bu_3SnH than it would with the negatively charged, highly nucleophilic, superoxide anion generated within a close contact ion pair. Moreover, if such a superoxide union did occur, then naturally, oxidative cleavage of the alkene component would inevitably ensue and, if this did not occur, then the acetylene would almost certainly be returned! Thus, the Scheme 50 team's own claimed yields strongly refute their mechanistic proposition.[60]

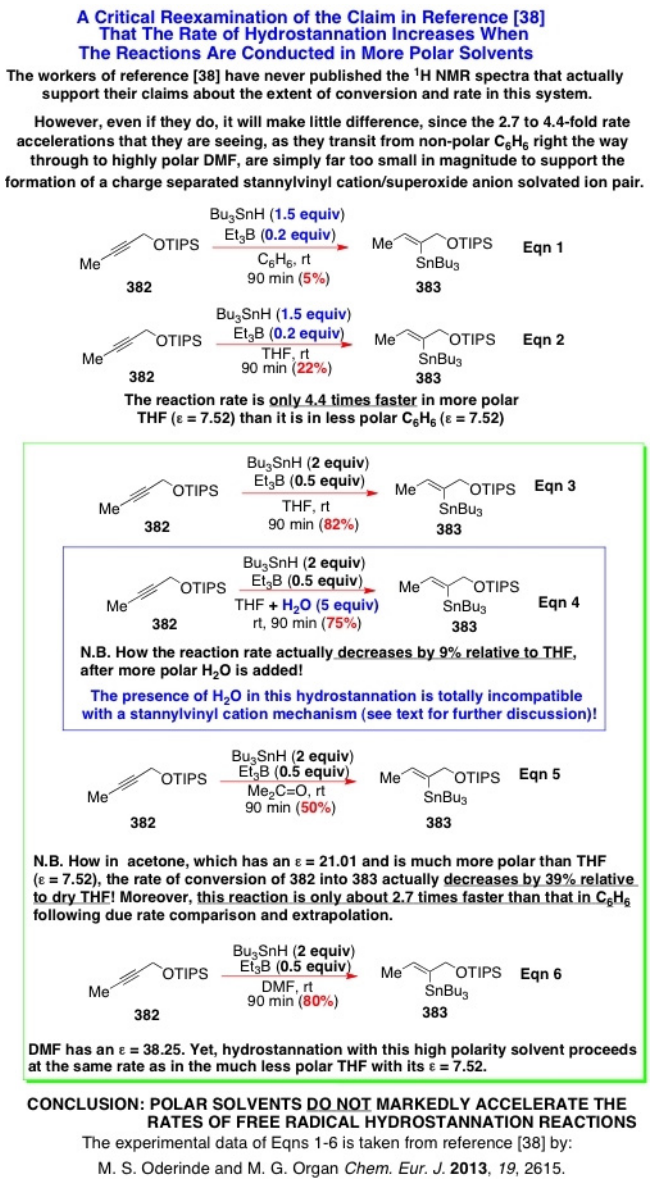
The Stang work[86] on alkynyl iodonium salt formation from alkynylstannanes has thus provided truly useful insights into how vinyl cations typically behave and react when they bear an adjacent α-trialkylstannyl substituent, and are exposed to a potent, negatively charged, nucleophile such as peroxide

anion. In this regard, they usually eliminate R_3Sn–Nu to give the alkyne. So, if the mechanism in Scheme 50[60] was operative, then one would inevitably expect the yields of hydrostannation to be poor with Ph_3SnH. However, we do not find that the yields of our alkyne free radical hydrostannations are typically poor when we use Ph_3SnH/cat. Et_3B and O_2 in PhMe. Not at all; in fact, the yields we obtain are usually very good, and only rarely do we ever see any starting acetylene present at reaction end.

Yet another point that we would like to make here is that our O-directed hydrostannation reaction with Ph_3SnH has now been successfully tested and applied on many different alkyl propargyl alcohol substrates, and the reactions have all proceeded very cleanly. If an α-triphenylstannylvinyl cation was involved in the reaction mechanism, then almost certainly, we and others would have noticed enol ether products arising (resulting from capture of the intermediary vinyl cations by pendant alcohol groupings), or allene-derived products.[87] However, not once have we encountered such products, nor has the Scheme 50[60] team.

A further point of contention, confusion and great experimental discord concerns the 2013 ACIE statement that was made by the reference [60] team *"that polar solvents accelerate Et_3B-mediated hydrostannylation of propargyl alcohols and their derivatives"*; which was subsequently paired with the second incorrect assertion that…… *"These results cast doubt on mechanisms proposing that AIBN and Et_3B-mediated alkyne hydrostannylation involves solely radical intermediates."*[60] ….. and the further erroneous statement that the mechanism of these reactions…….. *"could involve cationic intermediates whose formation would be favoured by polar solvents…."*.[60]

Given the significant opposition that this team has put up to our strongly experimentally supported (radical probe-based) free radical hydrostannation mechanism for propargylically-oxygenated dialkyl acetylenes,[29] we will now examine in detail the evidence that they have mustered to support their errant stannylvinyl cation mechanistic claim,[60,35] most notably the published polar solvent rate acceleration data that they have reported for the hydrostannation of **382** in different solvents (Scheme 65).[38] With regard to the latter,[38] not only will we show that their data is strongly in conflict with itself, it is also most unconvincing. Indeed, we would even go so far as to say that it lends no credible support to the stannylvinyl cation mechanistic hypothesis[60] that this team has consistently advanced for alkyne hydrostannation since 2013 (whose basic ideas have already been summarised by us in Scheme 50). Instead, if anything, the comparative solvent rate data that they report in reference [38] actually very strongly opposes the stannylvinyl cation mechanistic theory that they have put forward.[60] In light of this, we will now now reappraise their "pronounced" polar solvent rate acceleration data[38] for the hydrostannation of **382**, and we



Scheme 65. The published polar solvent-induced relative "rate acceleration" data for the hydrostannation of alkyne **382**.[38] Quite clearly, as the solvent polarity and dielectric constant increase from THF to aqueous THF and acetone, the "reaction rate" and extent of conversion of **382** into product actually *decreases* relative to that in dry THF. Note also how highly polar dry DMF (ε = 38.25) gives a similar rate and extent of conversion to dry THF of ε = 7.52 despite their vastly differing polarities. Significantly, highly polar acetone (ε = 21.01) only leads to a 2.7-fold increase in the hydrostannation reaction rate relative to non-polar benzene (ε = 2.25), while modest polarity THF is claimed to lead to a 4.4-fold increase in relative reaction rate; these solvent induced rate accelerations are just tiny. Such outcomes clearly show that the rate of free radical alkyne hydrostannation is most definitely not significantly or markedly accelerated by polar solvents, contrary to the assertions of references [38] and [60]. Additionally, the observation[38] that the product **383** still forms in the presence of H_2O irreconcilably conflicts with the mechanistic claim that this reaction proceeds through a stannylvinyl cation intermediate,[60] since such an intermediate would react rapidly with H_2O!

will show that the rate accelerations that they have observed are tiny and only compatible with a purely free radical mechanism of the type that we originally proposed[29] based on our 2005 work on **293** (Scheme 47).

Now although the community's attention was drawn[38] to the 4.4-fold increase in relative reaction rate (k_{REL}) and extent of product formation in the free radical hydrostannation of **382**, as the reference [38] workers moved from low polarity C_6H_6 to the slightly more polar THF (5% to 22% conversion after 90 min, Eqns 1 and 2, Scheme 65), in physical organic chemistry mechanistic terms, this level of relative rate acceleration is only miniscule.[38] It is far too small to be considered to be providing good solid experimental support for the formation of a highly charged stannylvinyl cation/superoxide anion contact ion pair of the type that has been suggested to form in Scheme 50,[60,35a] and it certainly does not amount to *"a remarkable increase in the rate of hydrostannylation using nBu$_3$SnH"* as was inaccurately stated by the workers of reference [38].

Besides, when discussing Eqn 3 in Scheme 65,[38] this team failed to recognise that when they recorded this greatly improved 82% conversion of **382** into **383**, they did actually markedly increase two other key reaction parameters, *viz.*, the amount of initiator that was present, and the amount of stannane. As regards the Et_3B, its quantity had more than doubled from 0.2 equiv. to 0.5 equiv. on this run, while the amount of Bu_3SnH had also increased from 1.5 equiv. to 2 equiv, when compared with Eqns 1 and 2. The net result was a greatly enhanced conversion of **382** into **383** over 90 min. Given the substantial increase in both the stannane and initiator concentration at the outset of this run, it is not surprising that such an increase in the relative reaction rate and the degree of conversion was observed under such circumstances (Eqn 3, Scheme 65). Moreover, this observed degree of change in the reaction rate and outcome is not so much a reflection of any specific solvent effect arising from working in the slightly more polar solvent THF of dielectric constant $\varepsilon = 7.52$, which compares with an ε of 2.25 for benzene, but rather the greatly increased quantities of reagents that had been added to the reaction mixture in Eqn 3, which made the forward reaction far more favourable than the ones in Eqns 1 and 2 which employed lower quantities of these reagents.

Now if we move on to consider what subsequently happened when the quantities of these two reagents were kept constant at 2 equiv. of Bu_3SnH and 0.5 equiv. of Et_3B in THF, but H_2O (5 equiv) was now added to the reaction mixture (see Eqn 4, Scheme 65),[38] what we now see is that the rate and extent of conversion of the alkyne **382** into the vinylstannane **383** *actually dropped* from 82% to 75% in this new much more polar solvent mix after 90 min. In other words, the reaction was found to be 9% *slower* in aqueous THF than it was in dry THF.

Likewise, if we also examine yet another reported run in Scheme 65,[38] on this occasion with 2 equiv. of Bu_3SnH and 0.5 equiv. of Et_3B in the solvent $Me_2C{=}O$ (acetone) for 90 min, yet again, we see an even more dramatic decrease in the overall reaction rate and extent of conversion of alkyne **382** into the vinylstannane **383** relative to dry THF. Specifically, we see the NMR yield and extent of conversion of **382** into **383** dropping from 82% in the much less polar dry THF to 50% in the much more polar solvent, acetone, and once again this is after the reaction had been conducted for 90 min at rt (see Scheme 65, Eqn 5).

The % yield figures supplied by the workers of reference [38] for the conversion of **382** into **383** indicate that there was a 39% decrease in the relative overall reaction rate when the reaction was conducted in the much more polar solvent acetone, when compared with the reaction run in dry THF. In other words, based upon their own published relative rate data,[38] as the reference [38] reporting team moved from THF to acetone, under otherwise identical reaction conditions, they saw that the hydrostannation of **382** actually proceeded much more slowly and at only 61% of the speed of the reaction in dry THF.

Now given the way in which the authors of reference [38] have gathered and presented their hydrostannation rate data on **382**, it has been necessary for us to do a calculated estimate of their data, to allow a crude rate comparison between THF, acetone and benzene under the conditions of Eqns 1 and 2 in Scheme 65, and we recognise that this is far from ideal.

Nevertheless, if we again assume that the hydrostannation of **382** in acetone proceeds at 61% of the rate of that in THF (and we appreciate the weaknesses of making such an assumption), then this allows one to roughly estimate that if the hydrostannation of **382** was conducted in acetone under identical conditions to those Eqns 1 and 2, the extent of conversion into **383** would likely be 13.42% after 90 min which, relatively, is only 2.7 times faster than the 5% extent of conversion in C_6H_6 under identical circumstances, which is much less of a rate increase than that seen upon moving from C_6H_6 to THF.

Now to assist readers with their analysis of the acetone/THF results, the dielectric constant (ε) of THF is 7.52, while that for acetone is 21.01. In other words, acetone, with its much higher dielectric constant, is much more polar than is THF, and it should therefore potentially be a much better solvent at stabilising a charged ion pair (if one was being formed). The use of acetone as the reaction solvent should, according to the Scheme 50 team's mechanistic analysis,[60,38a] have markedly increased the rate of hydrostannation of **382** with Bu_3SnH/Et_3B, if their 2013 mechanism held true, and

their polar solvent rate acceleration effect was genuinely significant and "pronounced", as they have stated in the title of reference [38].

The facts are, however, that the rate of hydrostannation of **382** in more polar acetone was actually slower than the rate in less polar dry THF, and this should have immediately raised concerns with this team about the overall validity of their claim of a "pronounced" polar solvent rate acceleration effect. While there is a very small rate increase in both cases relative to benzene, it is only a very tiny rate increase, and one that suggests that the effect of solvent on reaction rate is extremely small; negligible in fact.

On top of this, why would less polar THF cause a bigger rate increase than much more polar acetone, if solvent polarity effects were indeed genuinely important, and the Scheme 50 ionic stannylvinyl cation mechanism[60,35a] was operating? It does not make any sense at all, and certainly the workers who have gathered this data have not provided any rational explanation for this anomalous pair of results, nor for the remaining farrago of unusual rate data that they have collected,[38] which is neither backed up by spectra nor appropriate explanatory qualifying discussion.

Indeed, no mention is made whatsoever of this overall drop in the reaction rate and degree of conversion for the Bu_3SnH/Et_3B mediated hydrostannation of **382** in acetone or aqueous THF (relative to dry THF) in the second ACIE[60] follow-up publication that appeared (which was the first paper where these workers actually put forward their new stannylvinyl cation mechanistic hypothesis for alkyne hydrostannation).

Instead, the Scheme 50/reference [60] team just maintained that their new cationic mechanism for alkyne hydrostannation[60] had been solidly supported by a substantial polar solvent rate acceleration effect that included all of the rate measurements that had previously appeared in this prior 2013 *Chem. Eur J.* paper,[38] which encompassed the data that we have just presented in Scheme 65 amongst the offered experimental evidence.

It is probably fair to say that most teams who had observed such a decrease in the rate of hydrostannation for **382** on moving from THF to the much more polar solvent mix of THF and H_2O, or acetone, would instantly have recognised that any genuine claim to the existence of a coherent polar solvent rate acceleration effect in their alkyne hydrostannation reactions had immediately been rendered invalid by these experimental outcomes, which seemingly run counter to the claim of a general and consistent "pronounced" polar solvent rate acceleration effect for alkyne hydrostannation.[38,60]

Yet, notwithstanding the fact that the reference [38] team had themselves witnessed this noticeable drop in reaction rate and conversion (a 32% decrease in reaction conversion, and a 39% overall reduction in relative reaction rate) on moving from THF to the much more polar solvent acetone, they apparently thought that this reduction in reaction rate in Me_2CO was some form of less important, anomalous, result that could easily be overlooked, as could their aqueous THF hydrostannation rate retardation data, both of which went completely unexplained.

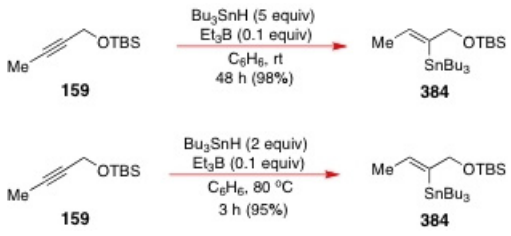
This is despite the fact that these two pieces of rate retardation data actually provide very important clues as to the lack of a marked polar solvent rate acceleration effect operating in these hydrostannation experiments.

By now, most physical organic chemists will recognise that the reference [38] claim of a "pronounced" hydrostannation rate acceleration effect in polar solvent media is invalid, particularly if one also considers the reported hydrostannation outcome for **382** in DMF[38] (Scheme 65, run 6) where an 80% conversion was recorded after 90 min at rt with Et_3B (0.5 equiv) and Bu_3SnH (2 equiv). Significantly, this conversion was just 2% lower than the one obtained in dry THF. Yet, DMF is a vastly more polar solvent than THF, it having a dielectric constant of $\varepsilon = 38.25$, which compares with an ε of 7.52 for THF. It would thus appear that massively increased solvent polarity is having very little effect on accelerating the rate of this hydrostannation reaction relative to dry THF.

While the relative rates of hydrostannation of **382** in THF and DMF are indeed approximately 4-fold greater than that in C_6H_6 (see Eqns 1 and 2 in Scheme 65, and then extrapolate), we have calculated that the rate of hydrostannation of **382** in acetone is only 2.7 times faster than that in C_6H_6 under identical circumstances. Clearly this claimed "pronounced" polar solvent rate acceleration effect is in fact insubstantial and essentially next to nothing. While such tiny increases in the overall reaction rate might indeed be genuine on each occasion, given their extremely small magnitude, they cannot possibly be considered to be providing firm mechanistic support in favour of the ionic mechanism envisaged in Scheme 50. Indeed, such tiny changes in the relative rate accelerations can also easily be attributed to a host of other factors that can include the polarisability of the solvents, or to variations in the cohesive energies and viscosities of the solvents. These minor variations in reaction rate could also be attributed to poor reagent quality on some runs, to variations in the reaction temperature, to the pre-existing O_2 content of the solvents, the alkyne samples and/or the reagents, or to inadvertant sunlight exposure, or even to errant or variable experimental technique. In addition, we do not know how many times these reactions were run or their general level of reproducibility. Such critical error analysis or internal assessment was totally absent from the relative rate determination work of reference [38], which is surprising given that so

much store was being placed upon this set of experiments to underpin the mechanistic theory of Scheme 50.[60,35]

Finally, we must draw the readership's attention to earlier work by the Organ group where it was reported that the alkyne **159** reacted with Bu_3SnH (5 equiv), Et_3B (0.1 equiv), and O_2 in C_6H_6 in 98% yield of the (*Z*)-isomer **384** after 48 h at 23 °C (Scheme 66).



Scheme 66. The Organ report of successful rt hydrostannations in C_6H_6.[36]

Additionally, these workers further observed that they could secure a near enough similar result in C_6H_6 (95% yield of **384**), if they reduced the amount of Bu_3SnH (2 equiv), Et_3B (0.1 equiv) and O_2 and simply heated the reactants to 80 °C for 3 h.

So, given the above reports, and the fact that a *massive* increase in relative reaction rate was *not* seen on transiting from C_6H_6 to: THF, acetone, aqueous THF, and highly polar DMF at rt, we simply do not consider that such minute polar solvent rate acceleration phenomena are providing the requisite firm experimental support needed to lend credibility to the 2013 stannylvinyl cation mechanistic claim for dialkyl acetylene hydrostannation with tin hydrides and cat. Et_3B/O_2 by the Scheme 50 team.[60,38] Rather, we believe that all of the experimental data[38] that they have marshalled actually very strongly opposes it and supports our own mechanistic position.[29]

Normally, when a reaction is accompanied by a significant increase in charge separation, as would be the case during the formation of a charged ion pair, such a reaction would generally have its rate *very profoundly* accelerated when it was conducted in a far more polar solvent of high dielectric constant, and when we say this, we are talking here about a k_{rel} or rate acceleration of at least many hundreds, if not thousands, or even hundreds of thousands, or millions of times. Three- to four-fold enhancements in reaction rate, of the type seen in reference [38], are just miniscule and are essentially negligible in the grand scheme of things. Indeed, if they do reveal anything at all, it is that an uncharged, non-polar, entirely free radical reaction pathway is likely operating in the alkyne hydrostannation process; one that is consistent with our own 2005 work[29] and one that does not significantly respond to dramatic increases in solvent polarity, which is precisely the opposite of what the proposers of the Scheme 50 mechanism are stating.[60]

The reference [60] workers have also failed to specify whether their stannylvinyl cation/superoxide anion partnership is formed either as a solvated contact ion pair, or as a solvent separated ion pair with a large distance between the two ions.[60] While clearly, in both cases, the resulting stannylvinyl cations would have to go on to ionically react with the tin hydride to satisfy their mechanistic suggestion, obviously the generation of a solvent separated ion pair would likely lead to even more dramatic and profound rate accelerations being observed in reactions run in solvents of high polarity and dielectric constant. The fact that such dramatic rate accelerations, of many hundreds if not thousands of times, were not reported in reference [38], very strongly refutes the mechanistic theory that has been put forward by these authors in references [60] and based upon their work in reference [38].

Indeed, for their proposed ionic reaction pathway to operate, it would require them to have observed much more substantive polar solvent induced rate accelerations, of many hundreds, thousands, or even hundreds of thousands of times. The facts are, however, that such dramatic or "pronounced" polar solvent rate accelerations were just not observed, which is precisely opposite to all of their strong assertions otherwise.[60,35a,38]

So, on the basis of all the highly conflicting rate and product conversion data of Scheme 65 (which is taken directly from the 2013 *Chem. Eur. J.* paper[38] published by this team), we consider that their later assertion that[60] *"….polar solvents accelerate Et_3B hydrostannylation of propargylic alcohols and their derivatives….."* to be one that is illusory and unconvincing in terms of the experimental support that it is providing for the stannylvinyl cation mechanistic hypothesis.[60,35] Indeed, if anything, the tiny solvent rate acceleration effects that they have observed[38] actually very strongly argue against this hypothesis, since their reaction rates are more than three to four or even five powers of ten too small to be indicative of a reaction pathway involving the formation of a contact or charge separated stannylvinyl cation/superoxide anion ion-pair. Instead, their claimed rate measurements are much more consistent with a largely uncharged, low polarity, entirely free radical homolytic mechanism for alkyne hydrostannation.

Now just to make sure that readers have full confidence in the integrity of what we are saying here with regard to the magnitudes of the polar solvent rate accelerations that one typically sees for reactions that proceed via a genuinely ionic mechanism, we now draw attention to the classic work of Huisgen,[88] who accurately determined the rate constants for the [2+2]-cycloaddition of tetracyanoethylene (TCNE) to ethyl isobutenyl ether in a range of solvents of vastly differing

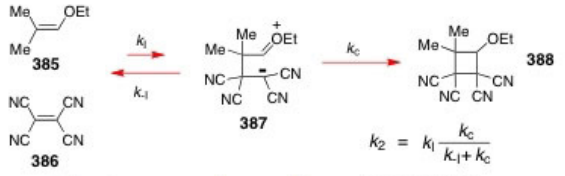
polarity (Table 2). It will soon be appreciated from a simple inspection of Table 2 that there was a 4,900-fold increase in reaction rate for this cycloaddition simply by changing the reaction solvent from non-polar CCl_4 ($\varepsilon = 2.24$, which is similar in polarity to C_6H_6) to highly polar MeCN ($\varepsilon = 36.64$, which has a polarity similar to DMF).

There was also a reasonable (though not perfect) correlation between increasing solvent polarity, as defined by ε, and the observed increase in rate, although Huisgen preferred to use another alternate measure of solvent polarity, the Dimroth-Reichardt parameter E_T, to more strongly emphasise the connection between increasing reaction rate and enhanced solvent polarity. However, it must be appreciated that there is *never* usually a perfect straight-line relationship between ε or E_T and log *k*, since the ion- and starting molecule-solvating ability, the solvent cohesive energy, and the polarisability of the solvent also often play a substantive role in determing the value of *k*!

Furthermore, and to even more strongly emphasise the point that we have made about the magnitudes of the rate accelerations that one should typically observe in highly polar solvents, particularly for reaction mechanisms where the degree of ionicity and charge separation increases as the reaction proceeds, we further draw attention to Huisgen's additional published rate constant ratios for a range of [2+2]-cycloaddition reactions conducted with TCNE in the highly polar solvent MeCN,[88,89,90,91] as compared with the rates in the non-polar solvents CCl_4 and cyclohexane ($\varepsilon = 2.02$) respectively (see Table 3). It can be seen that the observed rate accelerations are simply enormous on moving to MeCN!

Table 2. Huisgen's substantial rate accelerations for the highly ionic [2+2]-cycloaddition of tetracyanoethylene (TCNE) with ethyl isobutenyl ether in solvents of increasing polarity.[88]

Huisgen's Rate Constant Determinations for the [2+2]-Cycloadditions of TCNE with Ethyl Isobutenyl Ether in Solvents of Increasing Polarity

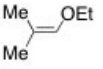
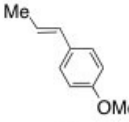
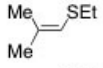
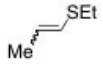
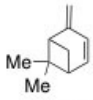


Solvent	ε	E_T	$10^3 k_2$ at 25 °C L mol^{-1} sec^{-1}
CCl_4	2.24	32.5	0.128
Cyclohexane	2.02	31.2	0.140
Et_2O	4.267	34.6	0.589
THF	7.52	37.4	5.55
$CHCl_3$	4.81	39.1	14.5
EtOAc	6.00	38.1	14.9
CH_2Cl_2	9.08	41.1	59.8
$Me_2C{=}O$	21.01	42.02	120
	26.00	42.0	284
MeCN	36.64	46.0	629

R. Huisgen *Pure & Appl. Chem.* **1980**, *52*, 2283.

Table 3. Huisgen's relative rate accelerations for the highly ionic [2+2]-cycloaddition of tetracyanoethylene (TCNE) with various alkenes in highly polar MeCN, compared with non-polar CCl_4 and cyclohexane.[88,89,90,91]

Ratios of the Rate Constants (i.e. the Relative Rate Accelerations) for the [2+2]-Cycloadditions of TCNE With Various Alkenes in Polar MeCN as Compared with Non-Polar Cyclohexane and CCl_4 at 25 °C

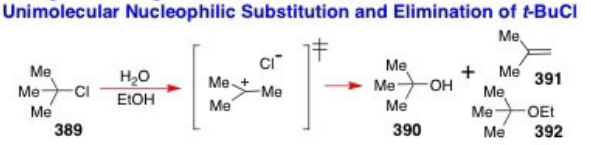
Alkene		k_{MeCN} / k_{CCl_4}	$k_{MeCN} / k_{Cyclohexane}$
		1700	2600
		4900	10800
		7800	29000
		17000	-
		2900	
	*cis*	17000	17000
	trans	16800	
		21000	54000

R. Huisgen *Pure & Appl. Chem.* **1980**, *52*, 2283.
R. Huisgen *Inorg. Chem. Acta* **1980**, *40*, X2-X4.
G. Steiner and R. Huisgen *J. Am. Chem. Soc.* **1973**, *95*, 5056.
H. Graf and R. Huisgen *J. Org. Chem.* **1979**, *44*, 2594.

Yet another piece of classic work that very clearly illustrates the high magnitudes of the polar solvent rate accelerations that one typically sees in organic reactions that have substantial ionic character is provided by Hughes and Ingold's magnificent 1948 study[92] of the hydrolysis of *t*-butyl chloride in aqueous EtOH, where unimolecular substitution and elimination (S_N1 and E1) both compete, and where a >750-fold rate acceleration of these reactions was measured as the % volume of polar H_2O in the aqueous EtOH was increased from 10% to 60% H_2O (see Table 4). It was Hughes alone who first spotted that the rate of hydrolysis of *t*-BuCl was greatly accelerated by increasing the quantity of water in the aqueous EtOH solvent mix, back in 1935.[93] It was also Hughes who first noted that the rate of hydrolysis of *t*-BuCl remained unaffected by the addition of dilute aq. KOH.[93a] The very fact that this unimolecular hydrolysis was

Table 4. Hughes and Ingold's observed 757-fold increase in reaction rate for the unimolecular substitution and elimination (S_N1 and E1) of *t*-BuCl in aqueous ethanol.[92,93] Note how the observed rate acceleration is generally massive for a genuinely ionic mechanism. This reaction was not accelerated by added $^-$OH.

Hughes and Ingold's Observed Solvent Effects on the Rate of Unimolecular Nucleophilic Substitution and Elimination of *t*-BuCl



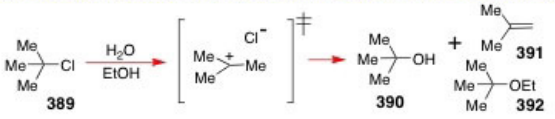
Vol. % H_2O in aqueous EtOH	10^6k_1 at 25 °C sec^{-1}	Solvent Polarity	Reaction Rate
10	1.71		
20	9.14		
30	40.3		
40	126		
50	367		
60	1294		
		Increases	Increases

N.B. The massive 757-fold increase in reaction rate observed upon transiting from 10% H_2O/EtOH to more polar 60% H_2O/EtOH.

K. A. Cooper, M. L. Dhar, E. D. Hughes, C. K. Ingold, B. J. McNulty and L. I. Woolf, *J. Chem. Soc.* **1948**, 2043.
L. C. Bateman, E. D. Hughes, C. K. Ingold, *J. Chem. Soc.* **1938**, 881.

Table 5. Fainberg and Winstein's repetition and further augmentation[94] of the Hughes and Ingold 1948 study on the unimolecular substitution and elimination (S_N1 and E1) of *t*-BuCl in aqueous ethanol. Note how Fainberg and Winstein observed an 850-fold rate acceleration on transiting from 10% H_2O in EtOH to 60% H_2O in EtOH, which is very close to Hughes and Ingold's 757-fold observed rate increase. Significantly, as well, Winstein and Fainberg observed a 98,497-fold increase in rate as they moved from 2% H_2O in EtOH to 90% H_2O in EtOH, so confirming Hughes and Ingold's polar solvent rate acceleration theory and their proposal of an ionic mechanism for this reaction.

Winstein and Fainberg's Observed Solvent Effects on the Rate of Unimolecular Nucleophilic Substitution and Elimination of *t*-BuCl



Vol. % H_2O in aqueous EtOH	10^5k_1 at 25 °C sec^{-1}	Solvent Polarity	Reaction Rate
2	0.0193		
10	0.166		
20	0.926		
30	3.65		
40	12.32		
50	40.4		
60	141		
70	488		
75	750		
80	1043		
90	1901	Increases	Increases

N.B. The massive 6283-fold increase in the reaction rate observed upon transiting from 10% H_2O/EtOH to more polar 80% H_2O/EtOH. Even more spectacular is the 98,497-fold increase in reaction rate upon moving from 2% H_2O in EtOH to 90% H_2O in EtOH.

A. H. Fainberg and S. Winstein, *J. Am. Chem. Soc.* **1956**, *78*, 2770.

found to be zero order in hydroxide by Hughes, demonstrated that it had to be the change in the polarity of the solvent medium and the addition of H_2O that was responsible for the observed rate accelerations seen. Such a situation did not pertain when 0.07 M aq. NaOH was added to MeBr or EtBr in 80% aq. EtOH at 55 °C, where 6000-fold and 1230-fold increases in S_N2 solvolysis rate were observed.[93b] These 1935 and 1940 observations of Hughes and Ingold were ultimately put onto an even firmer footing by the later 1948 work[92] of Table 4, which now accurately quantified the level of solvent rate acceleration for *t*-BuCl under such conditions. This study also further reinforced the new Ingold-Hughes theory for how polar solvents accelerate the rate of reactions with high ionic character; a theory which others have built upon ever since, including Winstein[94] (see Table 5) and Huisgen.[88,89,90,91]

With regard to Winstein and Fainberg's 1956 reinvestigation[94] and augmentation of the Hughes-Ingold *t*-BuCl hydrolysis rate study,[92] it will be noted that the Winstein rate data closely mirrored the data of Hughes and Ingold, certainly in terms of the magnitudes of the rate accelerations that were being observed upon moving from 10% H_2O in EtOH to 60% H_2O in EtOH (an 850-fold increase in rate was found by Winstein[94] vs Ingold and Hughes' >750-fold rate increase[92]). Winstein also noted that there was a 98,497-fold increase in the reaction rate upon moving from 2% H_2O in EtOH to 90% H_2O in EtOH. Now these are the sorts of large relative rate acceleration that the authors of references [38] and [60] would need to have seen as they moved to more polar solvent media, for their ionic mechanism of Scheme 50 to hold any semblance of credibility!

Now just to show how useful the observation of even miniscule rate accelerations can actually be in highly polar solvents with regard to ruling out an ionic reaction pathway, we thought that we would would showcase the classic Diels-Alder reaction example that can be found in Professor Neil Isaacs' book *Physical Organic Chemistry*[95] where the rate of cycloaddition between isoprene and maleic anhydride was compared in both acetonitrile and cyclohexane and found to be only 1.5 times faster in the former solvent. The very fact that this change to the much more polar solvent MeCN did not bring about a massive increase in reaction rate, but instead only a tiny rate increase, immediately ruled out the polar ionic pathway shown in Scheme 67 involving the charged dipolar intermediate **397**.

This work was also reinforced by Professor Michael Dewar's even earlier results on the Diels-Alder reaction, where again only small rate accelerations were found on moving to more polar solvents.[96] Again, this showed that the reaction

must be proceeding via a transition state that is not that different from the initial starting diene and dienophile in terms of dipolar character or charge.

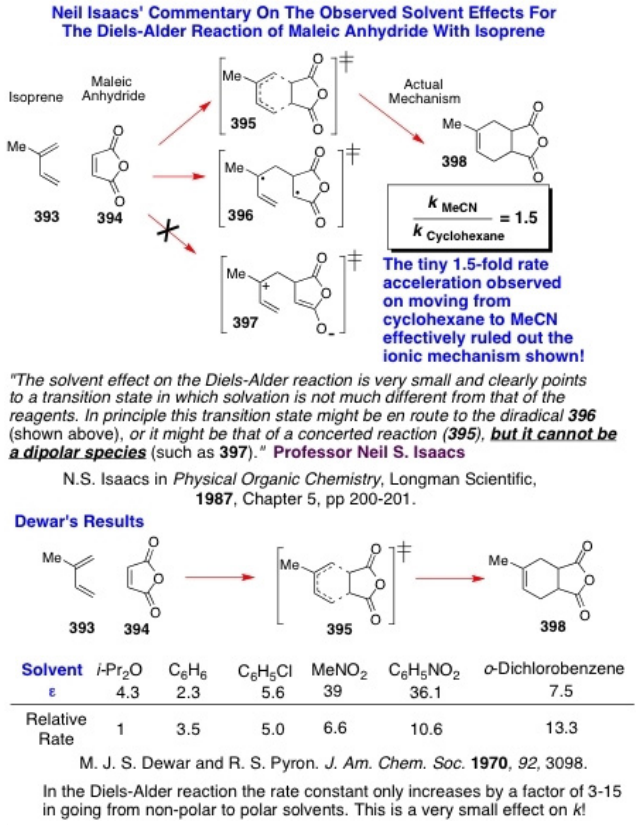
Even more striking than the results of Huisgen, Hughes and Ingold, and Winstein in Tables 2–5 are the phenomenal rate accelerations that were seen by Cram and coworkers[97] for the racemisation of (+)-2-methyl-3-phenyl-propionitrile in DMSO compared with MeOH, where a 1.4 million-fold rate acceleration was observed upon moving from neat MeOH as reaction solvent to 3% MeOH/97% DMSO (Scheme 68). This is, of course, reflective of the fact that a highly charged nitrilium anion **400** is being generated as an intermediate.

We specifically highlight these earlier studies and pronouncements of Ingold and Hughes,[92,93] Huisgen,[88,89,90,91] Isaacs,[95] Dewar[96] and Cram[97] since they very beautifully illustrate the large magnitudes of polar solvent induced rate acceleration that one must typically see before one can confidently say that a mechanism has high ionic character.

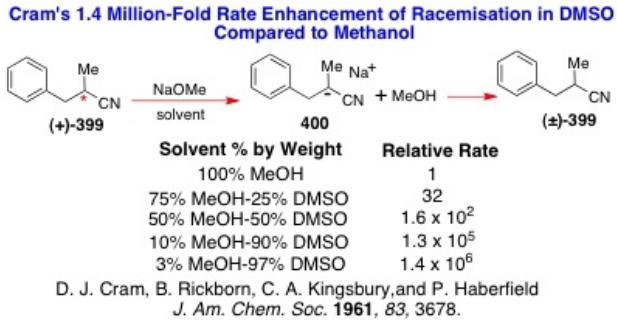
Quite clearly, the reported rate accelerations[38] in the free radical hydrostannation of **382** are far too tiny to lend any credible support to the claim that a stannylvinyl cation-superoxide anion ion pair[60] is being formed in this reaction. In fact the very small solvent-induced rate accelerations that have been seen[38] in the hydrostannation of **382** effectively nullify and revoke such an ionic mechanism with total certainty. Indeed, the published rate data is far more consistent with this reaction being one that involves purely free radical transition states.

We felt it necessary to include the polar solvent rate acceleration data of Hughes, Ingold, Huisgen, Isaacs and Cram in this Personal Account to put this landmark work firmly back in the public eye, since it appears that many in the field currently do not have any genuine idea about the magnitudes of the relative polar solvent rate accelerations that they must be seeing in order for them to be able to confidently assign an ionic mechanism to a specific reaction.

Moreover, such data should never be used singularly and in total isolation, but instead employed corroboratively, alongside other good mechanistic evidence and observations. While in the present instance, the authors of reference [60] did indeed attempt to marshal other data to support their ionic mechanistic proposal, that data was only singular in its nature, consisting of a lone DFT study performed in the gas phase, C_6H_6, and in THF that we feel has been misinterpreted.[60] Although this was actually sufficient to tell these workers that their stannylvinyl cation hypothesis was fundamentally flawed, due to the $+110.46\ kcal\ mol^{-1}$ (gas phase) and $+47.7\ kcal\ mol^{-1}$ (C_6H_6) inputs of energy that it required to bring about formation of the stannylvinyl cation **402** from the stannylvinyl radical **401** at rt (Scheme 69), nonetheless, they simply chose to ignore this tell-tale evidence, despite these calculations producing figures close to Alabugin's later values of $+100.1\ kcal\ mol^{-1}$ (gas phase), and $+50.5\ kcal\ mol^{-1}$ (PhMe), for the related conversion of **327** into **328** at 110 °C (see Scheme 53).[71] The reference [60]

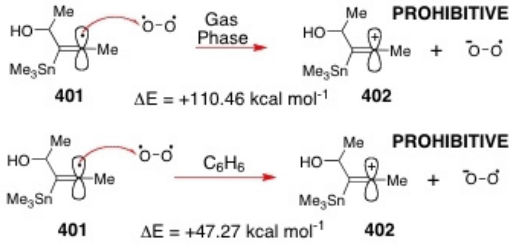


Scheme 67. Professor Neil Isaacs' brilliant analysis[95] of how the tiny 1.5-fold rate acceleration seen in the above DA reaction ruled out the intermediacy of **397**. Dewar's results[96] also support the Isaacs analysis.[95]



Scheme 68. Cram's finding[97] that highly polar 97% DMSO/3% MeOH massively increased the rate of racemisation of (+)-**399** by NaOMe; the rate increase is 1.4 million times faster than that in MeOH alone! Such a huge rate increase in this much more polar medium confirmed that this process had to be producing a solvent separated ion pair intermediate.

The Reference [60] DFT Calculations For the O_2-Mediated Conversion of a Stannylvinyl Radical into a Stannylvinyl Cation Reveal That The Process Is Highly Endothermic and Unfeasible in Both the Gas Phase and in C_6H_6

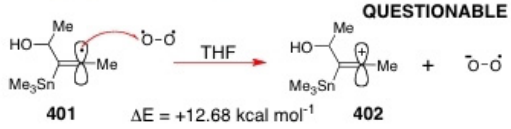


These energy inputs are prohibitive and the value obtained in C_6H_6 means that the process could not take place at room temperature!

Yet, Organ et al do many of their hydrostannations in C_6H_6 at rt.

M. S. Oderinde, R. D. J. Froese, and M. G. Organ, *Angew. Chem. Int. Ed.* **2013**, *52*, 11334.

The Reference [60] DFT Calculation For the O_2-Mediated Conversion of the Stannylvinyl Radical 401 into the Stannylvinyl Cation 402 in THF



While the authors of reference [60] have calculated an endothermic energy barrier of only +12.68 kcal mol^{-1} for O_2 to bring about this transition in THF, the PCM solvation programme that they have used to derive this value is notorious for giving faulty, inaccurate, ΔE values when highly coordinating THF is used as the reaction solvent!

Also, these workers do not show what role the THF is playing in bringing about this massive ΔE lowering event for the transition of **401** into **402**.

Due to other workers openly criticising the unreliable ΔE values that often emerge from such PCM solvation model DFT calculations conducted in THF, and the reference [60] team also not showing us how the THF lowers the energy barrier for this transition, we do not consider this energy barrier of ΔE = +12.68 kcal mol^{-1} to be at all reliable.

It is noteworthy that Alabugin et al do not use THF for their DFT calculations, but instead use PhMe, or alternatively they do their calculations in the gas phase which leads to much more reliable values.

M. S. Oderinde, R. D. J. Froese, and M. G. Organ, *Angew. Chem. Int. Ed.* **2013**, *52*, 11334.

Scheme 69. Here we present a key component of the reference [60] team's own DFT calculations on the O_2-mediated stannylvinyl radical to stannylvinyl cation transition.[60] Note how these were done on a linear configured stannylvinyl methyl radical **401** despite alkyl vinyl radicals being very well known to predominantly exist in a bent conformation. This fact notwithstanding, the ΔE values that they derived look far too prohibitive for this transition to occur. The limited nature of the Supporting Information that accompanies this paper has unfortunately made it very difficult for us to properly scrutinise these calculations in detail to assess their full veracity, but many of the intermediates in this paper look to be poorly represented structurally. These points aside, still, the claimed energy input required to achieve this electron transfer to O_2 in the gas phase and in benzene would be far too high to allow this transition to readily proceed at room temperature. Unfortunately, this has not been recognised, which has led to this team proposing this incorrect stannylvinyl cation mechanism for alkyne hydrostannation. Whether these calculations have been done correctly or not, still, a value of +47.27 kcal mol^{-1} for the transition of **401** into **402** in benzene should have alerted them to the problems with their new mechanistic scheme, since it meant that such an ionic mechanism could not be operating at rt. The ΔE value that they obtained in THF also looks to be anomalous when it is compared with the corresponding figure obtained in the gas phase; no explanation was offered for the huge drop in the ΔE value in this solvent.

data for formation of the stannylvinyl cation **402** in THF looks to be particularly shaky with respect to the ΔE value that it has yielded for this ionisation event, which, at +12.68 kcal mol^{-1} seems to be totally disparate from the gas phase value that they derived (+110.46 kcal mol^{-1}), which suggests that the THF figure is unreliable. It is also well known, within molecular modeling circles, that THF is a notoriously difficult solvent in which to do meaningful DFT calculations using the polarisation continuum model (PCM), and so no real confidence or store can be placed in the results that have been obtained using that particular solvent, certainly not with the computational programme that has been used by the reference [60] team, although Streitwieser's new hybrid density-functional programme mPW1PW91 might give better results in THF, if this data was to be subjected to informed thermal correction.[98] However, because of the coordinating properties of THF, and the intermediary stannylvinyl cation **401** providing multiple places for the THF to coordinate, it is difficult to accurately model the effect of THF in such a system. Certainly the reference [60] team's calculations provide very few clues as to what they actually did model to arrive at this astonishing THF ΔE figure for the conversion of **401** into **402** in Scheme 69. Indeed, after inspecting the experimental data that accompanies their paper, it is hard to see any role being played by the THF molecule in this massive energy lowering event. Additionally the 2013 calculations and mechanistic interpretations of the reference [60] team have all now been challenged and supplanted by Alabugin et al[71] who have done an entirely new set of calculations and interpretations in the gas phase and non-coordinating PhMe, and their conclusions all strongly disagree with the Scheme 50 team's hypothesis,[60,35] and support our own purely free radical O-directed mechanistic proposal of 2005 for alkyl acetylene hydrostannation under the Et_3B/O_2 rt initiated conditions in PhMe.[29]

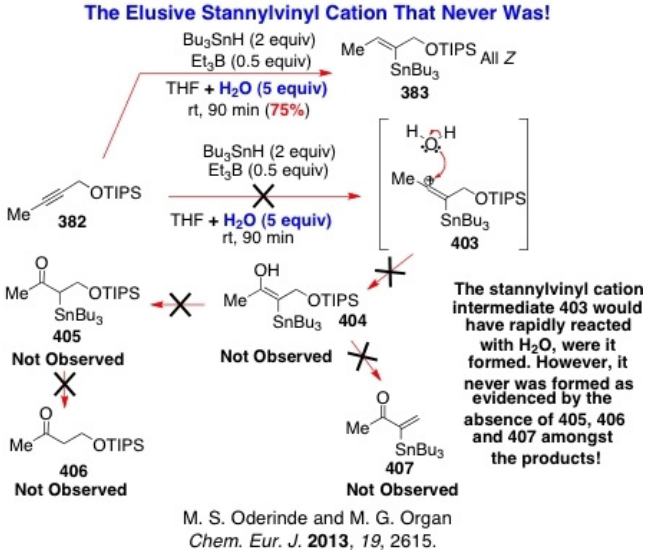
If we continue further with our reanalysis of the reported hydrostannation work of Scheme 65 on alkyne **382**,[38] but now consider it from a somewhat different theoretical perspective, we will see that this very same team have made yet another egregious misjudgement with respect to their experimental read-out of the hydrostannation that they conducted on **382** in aqueous THF (Scheme 65, Eqn 4). Specifically, they failed to recognise that if the highly reactive stannylvinyl cation **403** (Scheme 70) was being generated in such a solvent mix, it would almost certainly react rapidly with the added H_2O in that mixture, if the Scheme 50 mechanism of reference [60] was operational (see Scheme 70). Moreover, in so doing, it would produce a stannyl enol **404** which would subsequently protonate to give **405** or **406**, or β-eliminate the nearby OTIPS group to produce **407**. Additionally, such a H_2O trapping event would

probably occur at a much faster rate than a stannylvinyl cation ionic reduction with the Bu_3SnH that was present in much lower concentration.

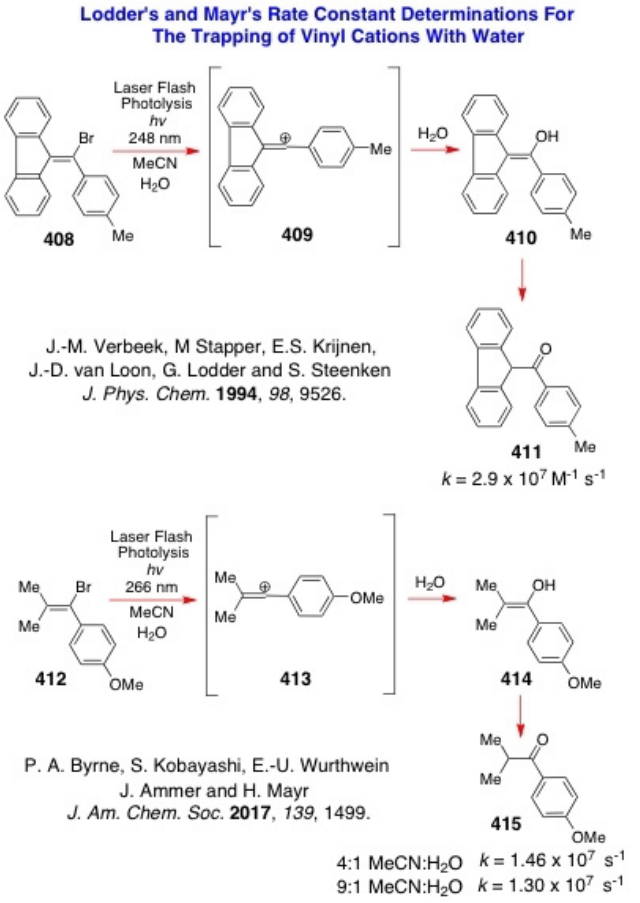
In this regard, Lodder et al have determined the rate constant for the reaction of the vinyl cation **409** with H_2O in MeCN to be $2.9 \times 10^7\ M^{-1}s^{-1}$ at 20 °C (Scheme 71).[76] Likewise, Mayr and coworkers have recently reported that the rate constant for trapping of the analogous vinyl cation **413** with H_2O is between 1.46×10^7 and $1.30 \times 10^7\ s^{-1}$ in MeCN/H_2O at 20 °C.[81] Both of these rate constant determinations indicate that the process of vinyl cation trapping by H_2O is usually quite fast.

Significantly, these vinyl cation trapping reactions of **409** and **413** with H_2O occur far more rapidly than the corresponding ionic reductions of the secondary carbocation **356** with Ph_3SnH and Bu_3SnH (Scheme 61), and Mayr has recently commented on how vinyl cations such as **409** and **413** have very similar reactivity profiles to diarylcarbenium ions in their reactions with nucleophiles.[81]

So, if the reference [60] team's stannylvinyl cation mechanism was correct and operational during this hydrostannation of **382** in aqueous THF, then this group would almost certainly have encountered ketone and enone products such as **405**, **406** and **407** in their reaction (Scheme 70), as it progressed, and they would almost certainly not have exclusively observed formation of the vinylstannane **383** as the major product of hydrostannation, as they did in 75% yield!



Scheme 70. The enol derived products **405**, **406** nor **407** were never observed during the hydrostannation of **382,** simply because the postulated stannylvinyl cation **403** was never formed during the hydrostannation event. In this regard, the above authors even go so far as to state: *"Importantly, the presence of water has little effect on hydrostannylation"*, attesting to the apparently clean identical outcome in both aqueous THF and in other anhydrous non-polar solvents such as PhMe or THF.



Scheme 71. Lodder and Mayr's independent rate constant determinations for the reactions of vinyl cations with H_2O; clearly, these are reactive intermediates.

The fact that the reference [38] workers made no mention of seeing anything other than **383** in their final published manuscript[38] (see Scheme 65) very forcefully argues against all of their subsequent stannylvinyl cation mechanistic claims in references [60] and [35a], and it shows that a fully free radical process must be operational in their reaction!

Alongside all of the above strongly opposing evidence to the very existence of stannylvinyl cation intermediates[60,35a] in free radical alkyne hydrostannations, such intermediates would be expected to be highly susceptible to undergoing competitive nucleophilic attack on the Sn group by the H_2O, and this mode of attack would likely proceed alongside the above enol trapping event. Such an attack of H_2O on Sn would, of course, be accompanied by a concomitant Stang elimination[86] (Scheme 64) of Bu_3SnOH to give back the starting acetylene **382** and would be accompanied by little overall reaction progression.

So together, the fact that the workers of reference [38] did not observe any ketone or stannyl enone products such as **405**, **406** and **407** in the hydrostannation of **382** conducted in THF/H_2O (Schemes 65 and 70), but instead, witnessed a very clean formation of the (*Z*)-vinylstannane **383** exclusively in 75% NMR yield very strongly argues that such a stannylvinyl cation cannot be a genuine intermediate in their reaction, and that the mechanism[60,35] of Scheme 50 is totally untenable, most especially when considered alongside all of the other opposing data that we have presented thus far.

So, rather than the reference [38] solvent rate data and their reaction comparisons in THF, and THF/H_2O, actually providing firm and solid experimental support for the claimed stannylvinyl cation mechanisic hypothesis of Scheme 50,[60] rather, we consider that their data and reaction outcomes both very strongly refute it.

Hopefully, the detailed analysis that we have provided herein will inform many future generations of organic chemists about how to correctly use polar solvent rate acceleration data to aid in successfully elucidating organic reaction mechanisms. If anything, our present article should provide important definitive guidance about the magnitude of relative polar solvent rate acceleration effects that one must typically observe before one can reasonably confidently ascribe an ionic path to an organic or organometallic reaction, with only very large relative rate accelerations ever being confirmative of an ionic pathway having been followed,[99] and even this conclusion must always be tempered and further backed up with other good mechanistic evidence before it can be accepted in the present day and age. Likewise, the same is true for the use of DFT calculations, which require a sensible input to be allied with a careful interpretation of the output, in order to yield genuinely meaningful mechanistic conclusions about the way in which a reaction works. What we have seen in Scheme 69[60] is a distinct lack of informed interpretation of both the input and the output, with devastating consequences for all concerned, but most especially ourselves, with the subsequent misinformation that it has unleashed.

It really is a very strong testament to the power and worth of the Hughes-Ingold theory of polar solvent rate acceleration, that now, 70 years on,[92,93] it is still playing such a substantive guiding role in helping to dismantle and stand down incorrect mechanistic theories. In the present instance, it is the stannylvinyl cation mechanism of Scheme 50[60,35a] that it has helped to refute, and we must therefore pay great tribute to these two great British UCL chemists for this, in this anniversary year of their landmark 1948 publication,[92] and also to Saul Winstein[94] for his reinforcement of the Hughes-Ingold theory, and to Rolf Huisgen's team who have also further expanded our knowledge of how polar solvents can profoundly affect reaction rate.[88,89,90,91] We cannot also forget the powerful contributions that have been made to this field by the great Professors Isaacs,[95] Dewar,[96] Cram,[97] and Christian Reichardt, who has authored many great publications on solvent effects.[99]

However, before we fully depart from our discussion of the topic of solvent effects in these free radical alkyne hydrostannylation reactions, we would like to draw attention to the fact that there is yet more solvent related evidence from the Organ team's own published work that very strongly opposes and compromises their recent stannylvinyl cation mechanistic claims,[60,35a] and this includes their reports of having achieved great success in their O-directed alkyl acetylene hydrostannations mediated by cat. Et_3B/O_2 in aromatic solvents such as C_6H_6 and PhMe!

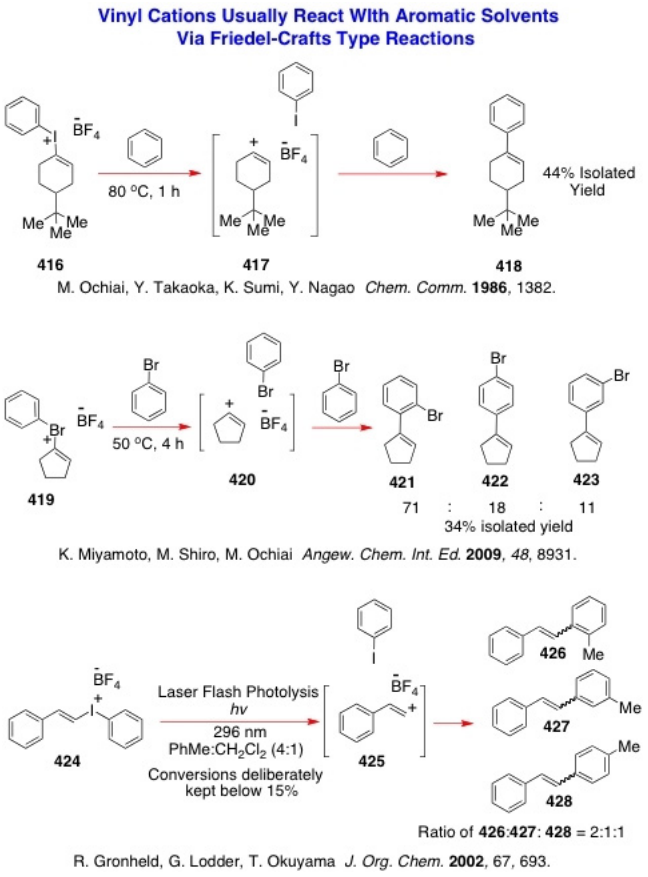
Past work from many other teams[100,101,102] has now unambiguously shown that when vinyl cations are generated in aromatic solvents such as C_6H_6 or PhMe, they generally always vinylate those solvents through an electrophilic aromatic substitution reaction, which produces arylated alkenes. Additionally, such products are usually easily isolated. Some examples of vinyl cations that have been found to react with aromatic solvents are listed in Scheme 72.

Therefore, for the authors of reference [36] to have reported at least 9 extremely high yields (>94%) in their (*Z*)-selective alkyne hydrostannation reactions with Bu_3SnH and Et_3B in C_6H_6, and have given no indication of having isolated or observed arylated tetrasubstituted vinylstannane products, or their proto-destannylated counterparts as by-products, this clearly provides further good opposing evidence against the intermediacy of a stannylvinyl cation intermediate in their O-directed free radical hydrostannation reactions. Indeed, it suggests that they simply cannot be genuine reaction intermediates in such processes.

Likewise, in all of the free radical hydrostannations that we have conducted with Ph_3SnH/cat. Et_3B/O_2 in PhMe, not once have we ever encountered a tolylated tetrasubstituted vinyl triphenylstannane product of any kind in our reaction mixtures, despite us running many such reactions on countless occasions, and us examining these mixtures very carefully every time.

Indeed, given that no group has ever witnessed a tetrasubstituted arylated vinylstannane (or an analogous arylated proto-destannylated product) being formed in a hydrostannation reaction conducted in an aromatic solvent, either under Et_3B or AIBN initiated free radical conditions, this means that it can be fairly safely concluded that the stannylvinyl cation hypothesis[60,35] of Scheme 50 is unviable and flawed.

So, to summarise, we have presented a vast mountain of truly strong theoretical and experimental evidence which all overturns the recent O_2-mediated α-stannylvinyl cation mechanistic proposal[60,35a,37] that has appeared for alkyl- and

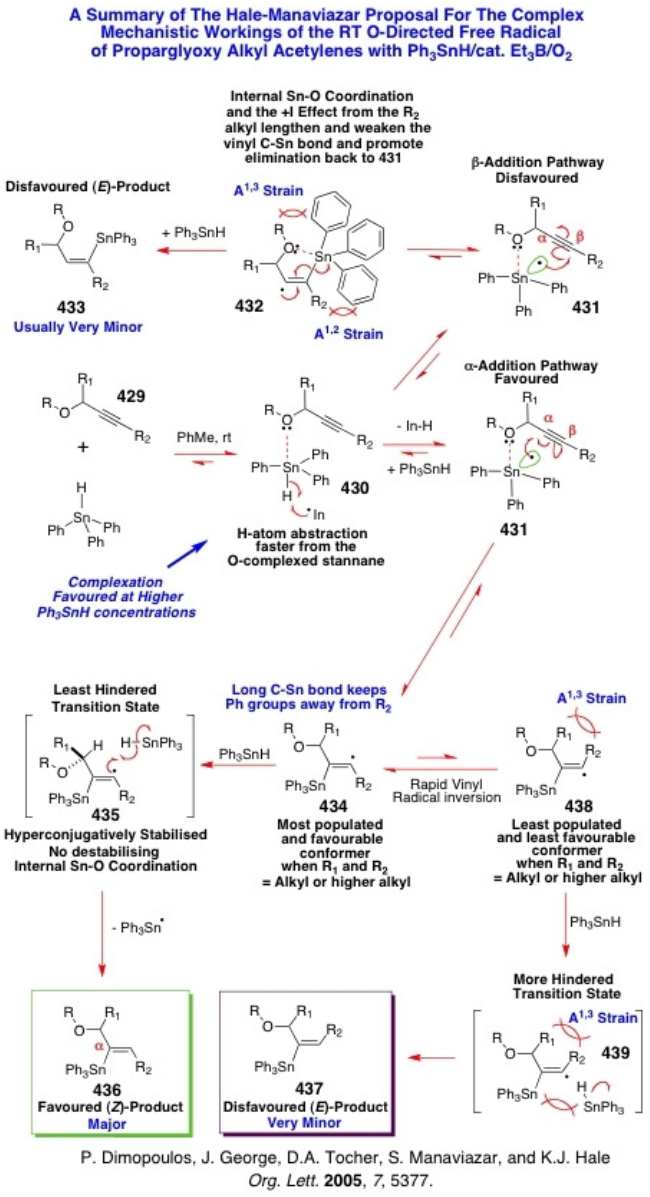


Scheme 72. Vinyl cations typically undergo Friedel-Crafts alkylation in aromatic solvents.[100,101,102] Since we have never seen such an arylated vinylstannane in either PhMe or C_6H_6 when we have performed our O-directed free radical hydrostannations with Ph_3SnH or Bu_3SnH/cat. Et_3B in these solvents, this further indicates that a stannylvinyl cation cannot possibly be forming in these hydrostannation reactions, and such evidence clearly opposes the mechanistic thinking of references [60] and [35] that such intermediates are being generated.

aryl-acetylene hydrostannation. We have also demonstrated here that the greater majority of this opposing evidence already existed in the literature long before this incorrect mechanistic theory was put forward in 2013.[60] Due to the incongruous and seriously faulty nature of this 2013 mechanism, and the fact that it has continued to be left in the literature, despite two recent papers highlighting its problems,[59,71] we feel that the community should heretoforth disregard it, due to the fact that it is not backed up by one single credible piece of supporting experimental evidence, and it is opposed by a legion of good mechanistic work and countering experimental observations that all very strongly refute it. Besides, the computational calculations[60] that have been claimed to support this mechanism, appear to be defective and misinterpreted, most especially the THF results that have been obtained. Indeed their subsequent conclusions have all recently been challenged and overturned by the Alabugin group, whose later 2015 calculations[71] and conclusions are all fully aligned with the numerous previously published experimental facts and results that have been gathered in this field to date. Additionally, Curran and McFadden[59] have also recently criticised the stannyvinyl cation mechanistic scheme of reference [60], stating that…*"the unusual observations of Organ and coworkers do not demand new mechanistic pathways or new intermediates in the Et_3B/O_2 initiated hydrostannation of propargyl silyl ethers"*. We fully concur with that general view.

Accordingly, we now reinstate here the O-directed free radical mechanism that we originally proposed in 2005 for the reaction of propargylically-oxygenated alkyl acetylenes with Ph_3SnH/cat. Et_3B/O_2 in PhMe (Scheme 73), which was never actually withdrawn by us.[23,29] This mechanism satisfactorily accommodates all of the published experimental evidence and observations that have been made in the field to date by all of the groups who have studied these reactions in detail. It not only credibly explains the observed regiochemical outcome of these processes, which must be O-directed and entirely free radical for the reasons we have outlined, it also rationally explains their preferred stereochemical outcomes as well.

Our mechanism (Scheme 73) recognises that the intermediary α-stannylvinyl radicals that will form will rapidly invert between the (*E*)- and (*Z*)-isomeric forms and essentially have bent structures, with the most heavily populated invertomer being the (*Z*)-isomer **434**, due to the significant $A^{1,3}$-strain that will be present in its (*E*)-configured counterpart **438**, as was first proposed by us in 2005.[29,23] We suggest that H-atom abstraction will occur preferentially from the (Z)-vinyl radical **434** in the manner shown due to transition state **435** offering the least hindered pathway for approach by the bulky Ph_3SnH. Our mechanistic proposal also strongly argues that the primary reason why the β-alkyl-β-stannylvinyl radicals of structure **432** are not long-lived in solution is because of combined $A^{1,2}$ and $A^{1,3}$ repulsions operating alongside significant internal O–Sn coordination and +I electron donation from the β-alkyl group. The latter two phenomena will help to collectively lengthen and weaken the C–Sn bond of any initially formed β-alkyl-β-stannylvinyl radical **432**, to help promote its rapid dissociative elimination back into the O-coordinated stannyl radical of structure **431** from which it originated. Our proposed mechanism also invokes no such internal O–Sn coordination occurring in the (*Z*)/(*E*) α-stannylvinyl radicals **434** and **438** that are being formed, which confers on the preferred invertomer **434** the necessary longevity to allow it to engage in a fast irreversible H-atom abstraction from the stannane to give the observed major product **436**. Moreover, if **434** does eliminate a Ph_3Sn radical, its very close proximity to the propargyl O-atom will



Scheme 73. The primary mechanism of the rt O-directed free radical hydrostannation with Ph_3SnH/cat. Et_3B/O_2 in PhMe.[23,29]

probably ensure that it is quickly recaptured to regenerate **431** and, if it does not, it will probably serve to mediate a separate cascade of H-atom abstraction events from stannane in the solution, until eventually another complex of **430** will have its Sn–H bond homolytically cleaved to generate a new **431** entity ready to propagate the desired radical addition chain to generate more **436** preferentially.

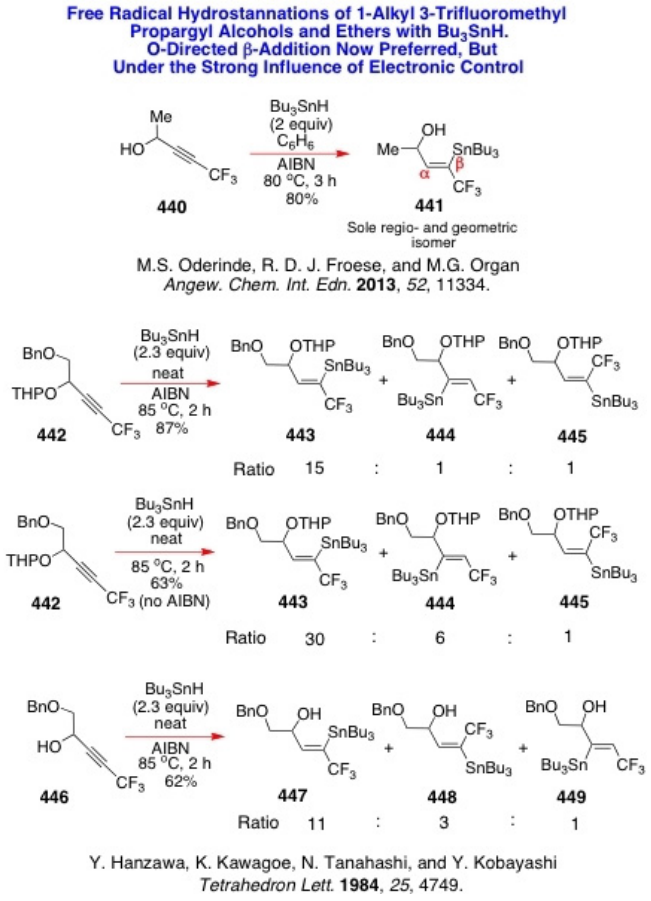
The aforementioned mechanism fits *all* of the known experimental observations that have been made to date, and it does not violate the Principle of Least Nuclear Motion,[77] unlike its Scheme 50 stannylvinyl cation alternative,[60] which would require many high energy steps to be effected in succession for it to proceed.

With regard to the latter, and to also explain the differing regiochemistry observed by the authors of reference [60] in the free radical hydrostannation of **440** (Scheme 74), and that by Kobayashi[61] with **442** and **446** even earlier in 1984, we now suggest that the preferential formation of the β-adducts in these systems is actually due to the stannyl radical β-addition process being simultaneously electronically-guided and O-directed, in alkyne systems where a trifluoromethyl unit is connected to the propargylically-oxygenated acetylene.

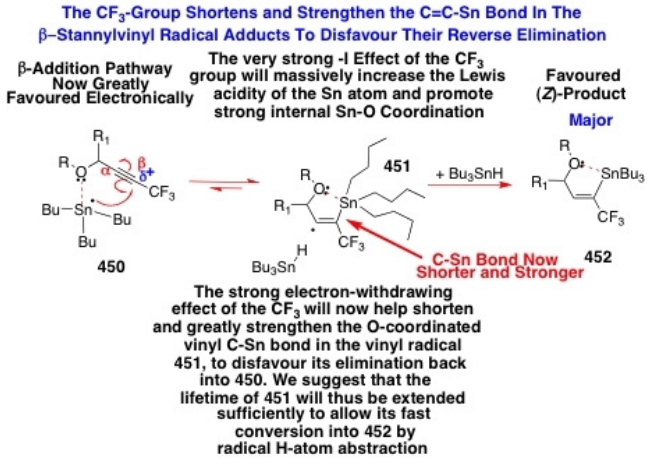
More specifically, it will be remembered that β-O-directed free radical hydrostannation with R_3SnH reagents is actually the normal, kinetically-controlled, course of events reported for propargylically-oxygenated *terminal* alkynes, when the reactions are conducted carefully; this outcome was first reported by Corey, Willem and Gielen, Wang, Dussault and others in various publications (highlighted in Schemes 1 and 10). It is also well documented in the literature that trifluoromethylated alkyl- and aryl-acetylenes are a unique and special class of substrate that are highly subject to electronic control in their free radical hydrostannation reactions. However, the manifestation of these effects is still not properly understood.

How we rationalise the preferred outcomes with **440**, **442** and **446** is that when a strongly electron-withdrawing trifluoromethyl group is present on the β-acetylenic carbon, its strong -I effect renders the β-carbon very δ^+, so favouring attack by the O-coordinated nucleophilic Bu_3Sn radical at this position. We further contend that this strong -I and O–Sn coordinative effect will tend to persist post-addition, and that this will serve to simultaneously shorten and strengthen the O-coordinated C–Sn bond in the intermediary β-trifluoromethyl-β-tributylstannylvinyl radical **451** (Scheme 75). We further contend that this C–Sn bond strengthening event,[103,104,105] along with Sn-radical hyperconjugation,[29,71] will give this intermediate *a sufficiently extended lifetime* in solution for it to undergo fast H-atom abstraction to give **452** rather than undergoing the reverse elimination, as is the case when a β-alkyl group is present.

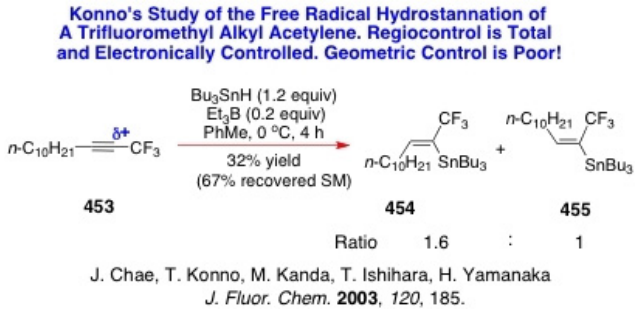
By way of contrast, when a +I alkyl group replaces the $-CF_3$, which is the situation for all of the systems that we have examined with Ph_3SnH, such +I groups will usually donate electron density towards the C-atom bearing the tin in the β-radical adducts **432** (Scheme 73). This would be predicted to cause a simultaneous bond lengthening and weakening of the O–Sn coordinated C–Sn bond, and promote subsequent eliminative reversal back to the parent alkyne O-coordinated stannyl radical **431** (see Scheme 73). We suggest that it is this O-coordinative C–Sn bond weakening effect in alkyl β-stannylvinyl radicals **432**, alongside the magnified $A^{1,2}$-strain effects at the β-carbon, which



Scheme 74. O-Directed free radical hydrostannations of 1-alkyl-3-trifluoromethyl propargyl alcohols and ethers with Bu_3SnH; note how β-addition is now always preferred in these systems.



Scheme 75. We suggest that the free radical hydrostannations of 1-alkyl-3-trifluoromethyl propargyl alcohols and ethers with Bu_3SnH is subject to both electronic control and O-coordinated stannyl radical addition control which synergise to give selectivity in favour of the observed vinylstannanes **452**.



Scheme 76. The free radical hydrostannation of a non-propargylically oxygenated 1-alkyl-3-trifluoromethyl acetylene with Bu_3SnH under cat. Et_3B initiated conditions.[62] Note how β-addition is still *exclusively* preferred, and how the H-atom abstraction step proceeds with poor *Z/E* selectivity due to the lack of internal O-coordinative control in the addition and H-atom abstraction steps. Note also the *very low yield* of this Bu_3SnH/cat. Et_3B mediated hydrostannation; this is quite typical for Bu_3SnH/cat. Et_3B mediated hydrostannations (vide infra).

collectively impart just enough instability to the resultant β-stannyl vinyl radicals to ultimately cause them to revert back to **431** by rapid reverse elimination, which ultimately serves to promote the observed α-stannylation outcome. It will be recalled that in this proposal α-stannyl-β-alkyl vinyl radical adducts will not be subject to any O-coordinative weakening following addition, *due to their structures being product-like*, and them not experiencing any such allyloxy Sn–O interactions in the radicals of structure **434**.

Clearly, in a system where a -I CF_3 group now replaces the β-alkyl on an β-alkyne carbon, this group will significantly magnify the Lewis acidity of the Sn group in the β-stannylvinyl radical adducts of structure **451** (Scheme 75), and this will help promote and preserve the internal O-coordination in such systems, even at higher temperatures, but without significantly lengthening and weakening the new C–Sn bond. Thus, we envision that this combined attractive effect will actually help to significantly prevent the vinyl radical **451** from eliminating to give the O-coordinated Sn radical **450**. Our strong emphasis on the importance of electronic influences in these quite special and unique trifluoromethyl alkyl acetylene systems derives from the 2003 work of Konno[62] who showed that the β-selectivity can be controlled *exclusively* by alkyne ground state polarity (see Scheme 76).

In fact, given Konno's observation[62] that the trifluoromethyl- acetylene system **453**, which lacks a propargyloxy group, gives rise to total β-regiocontrol, but very poor *Z/E* geometric control, when submitted to free radical hydrostannation with Bu_3SnH/cat. Et_3B, it is surprising to see that the authors of reference [60] could have rejected the possibility that an O-directed free radical hydrostannation might be helping to reinforce both the regiochemical and the

geometric outcome that they observed with **441**; indeed, it may possibly be helping to slow down the rate of vinyl radical inversion to favour H-atom abstraction from the internally O-coordinated (*Z*)-conformer **451**.

Moreover, given Alabugin's modelling[71] in Scheme 54, where distinct energetic benefits were found to be associated with O–Sn coordination in radical hydrostannation reactions of this sort, we believe that our *combined* electronic/R_3SnH O-coordinative mechanistic explanation best explains the Organ[60] and Kobayashi[61] observed geometric outcomes in alkyl trifluoromethylacetylenic alcohol and ether systems, most especially since a stabilising O–Sn coordinative effect would now be promoted by the presence of a CF_3-group on the β-vinylic C-atom bearing the Sn in vinyl radicals of structure **451**, and this stabilisation would occur right the way through the journey from starting acetylene into the product **452** (Scheme 75).

There is certainly no need to invoke a β-stannylvinyl cation in the Et_3B/O_2 or AIBN mediated reaction pathways to explain the outcomes in propargylically-oxygenated trifluoromethyl-acetylene systems, as has been done by the authors of reference [60]. Indeed their cationic mechanism really does not provide any rational explanation as to why only a single geometric isomer **441** should specifically form in their system, most especially with this particular geometry, *syn* to the hydroxy, whereas our modified electronic and O-directed free radical stannation mechanistic proposals do satisfactorily explain this outcome, and the related preferred outcomes with **443** and **447**.

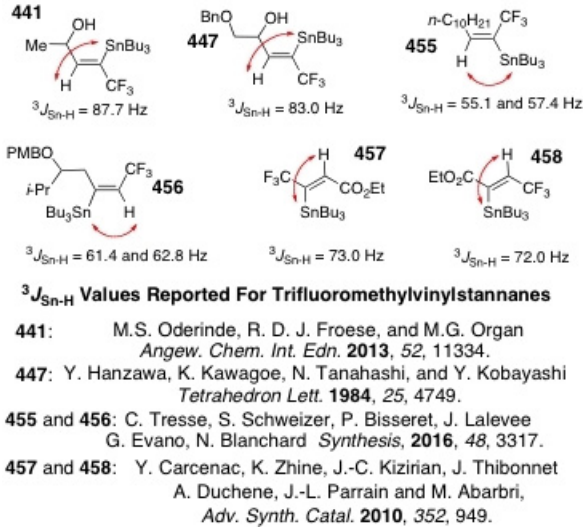
There is also every possibility that strong internal O-coordination might be strongly influencing the outcome of any isomerising tin radical additive-elimination to the (*E*)-vinylstannnane products that may be arising in these reactions to allow their facile conversion into their (*Z*)-counterparts.

Like ourselves, Konno et al[62] invoked a purely free radical mechanism to explain the reaction outcomes of their hydrostannations in alkyl and aryl trifluoromethyl-acetylene systems under these conditions. Given the low (*E*)/(*Z*) stereocontrol observed by Konno with **453**,[62] one would predict similar poor geometric selectivity for **440** (the reference [60] system), if an O-directed free radical hydrostannation event was not contributing significantly to the observed regio- and stereo-chemical outcome, and electronic factors were solely at play.

However, since the authors of reference [60] report that they have observed only one product from their alkyne system, and this product is **441**, where the OH group and the Bu_3Sn group are both *syn* to one another, this sole stereochemical preference very strongly argues in favour of the O–Sn coordinative mechanistic explanation that we have advocated, since no other proposal credibly explains this remarkable outcome alongside the results of Kobayashi.[61]

To add further weight to our proposition, we note here that strongly electron-withdrawing groups have long been known to shorten and strengthen adjacent bonds, with CF_3 having already been documented to increase the strength of adjacent C–H and C–C bonds by Friend and Napier[103] and also by Zhang.[104] We therefore feel that the O-directed β-stannylvinyl radical F_3CC–Sn bond shortening and bond strengthening hypothesis[105] is totally credible for explaining the observed preferred geometric outcomes with **440**, **442** and **446**.

Further evidence that very strong electronic influences are specifically at play in β-stannyl-β-trifluoromethyl alkenes comes from an inspection of the $^3J_{Sn-H}$ coupling constants for such systems (Scheme 77). Ordinarily in alkyl α- and β-stannyl alkenes, where the H–C=C–Sn relationship is *trans* the $^3J_{Sn-H}$ coupling constants are between 150–190 Hz,[23] while for the *cis* systems the $^3J_{Sn-H}$ coupling constants are typically between 80–100 Hz.[23] Strongly electropositive substituents on the C=C double bond will generally tend to greatly increase the *J* values,[72d] while strongly electronegative generally decrease the *J* values.[106,107] The influence that CF_3 groups have on the magnitudes of the $^3J_{Sn-H}$ coupling constants values is enormous, this group typically reducing the magnitude of the *J* value by half in both geometric isomers. Thus, in the *cis* systems **455** and **456**, the $^3J_{Sn-H}$ coupling constants are 55.1/57.4 Hz and 61.4/62.8 Hz respectively.[106] In the case of the *trans* systems **458** and **457** the $^3J_{Sn-H}$ coupling constants are 72 Hz and 73 Hz respectively. These values are clearly much lower than the system

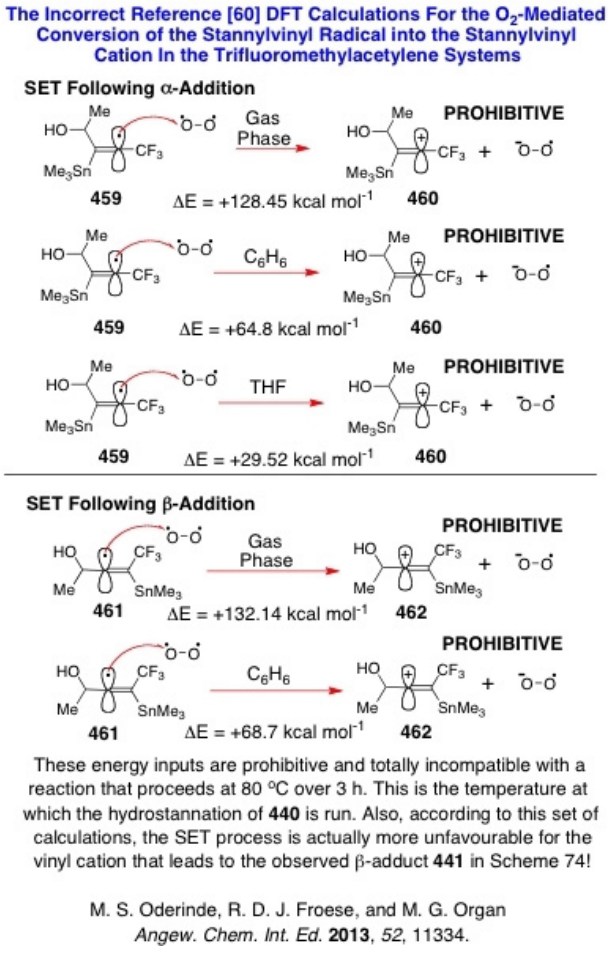


Scheme 77. A trifluoromethyl group on the C=C double bond of a vinylstannane dramatically reduces the magnitude of the $^3J_{Sn-H}$ coupling constant due to its strong inductive removal of electron density from neighbouring bonds.

441 prepared by Organ et al where the $^3J_{Sn-H}$ coupling constant was 87.7 Hz,[60] and Kobayashi's system **447** where the value was 83 Hz.[61] This further diminution of *J* in **457** and **458** is due to the additional electron-withdrawing $-CO_2Me$ being present.[106] However, these figures are still ca. 60 Hz smaller than if an alkyl group was present instead of a $-CF_3$. This massive decrease in the $^3J_{Sn-H}$ coupling constant in the β-stannyl-β-trifluoromethyl alkenes clearly shows how profoundly the $-CF_3$ group can withdraw electron density from connected C–C bonds, and undoubtedly the operation of such a powerful electronic effect will not only promote stannyl radical addition and bonding to an acetylenic carbon bearing such a CF_3 group, it will equally likely decrease the desire of the β-stannyl-β-trifluoromethyl-vinyl radicals to O-coordinatively eliminate once formed.

A further problem with the mechanistic proposal of reference [60] concerns the partially bridged stannyl cyclopropenium ion that it invokes.[60] We ourselves remain totally in the dark as to what geometry is actually being proposed here for this intermediate by these workers, which, as vaguely drawn out by them in their 2013 and 2014 papers,[60,35a] appears to have one of the alkene carbons adopting a linear geometry, and the other a highly distorted angularly strained arrangement. No clear rationale is provided for how this partially bridged common stannyl propenium ion arises nor how it gives the differing geometries of product, making the β-stannylvinyl cation proposal that they advance look even more questionable. In our view, the reference [60] mechanism is certainly not as logical and clear-cut as our own present unified O–Sn coordinative mechanistic proposal which is totally rational.

Another item of concern, raised by the DFT calculations of reference [60], relates to the stannylvinyl radical to stannylvinyl cation transition that is suggested to operate in the free radical hydrostannation of trifluoromethyl acetylene **440** (Schemes 74 and 78);[60] in particular the very high energy input that is required [+68.7 kcal mol^{-1} (2.98 eV)] for the O_2 mediated conversion of **461** into **462** in C_6H_6. Such a high energy input would, in all certainty, make this oxidation impossible to achieve in C_6H_6 at reflux, assuming, of course, that one accepts the reference [60] DFT calculations at face value. However, for the reasons that we have outlined above, it is our belief that these calculations have been incorrectly performed. We are also of the view that the magnitudes of the reference [60] ΔE values have been incorrectly assessed by this team, even if they do subsequently turn out to be correct in their magnitude. However, we very much doubt that they will ever be verified by other workers (see our accompanying commentary in Scheme 78 which highlights the problems that we have unearthed).



Scheme 78. The ΔE values that have been reported in reference [60] for the stannylvinyl radical to stannylvinyl cation transition of **461** into **462** (obtained using Density Functional Theory (DFT)) further call into question a stannylvinyl cation mechanism for the free radical hydrostannation of alkyne **440** to obtain **441** (Scheme 74). In this regard, the high endothermicity of this SET process means that the formation of such a cationic intermediate would simply not be feasible in C_6H_6 even at reflux. The added claim that the SET process is energetically lower for the **459** to **460** transition is equally untenable, since this would place the cation directly on the vinylic carbon bearing the electron-withdrawing CF_3 group. Clearly, this pathway would be of much higher energy than the one that converted **461** into **462**, which would localise the vinyl cation on the alkenic carbon atom attached to the less electronegative group. In our view, these DFT calculations of reference [60] are erroneous. They also deviate significantly from how this team discussed things in the main text and in Scheme 2 of their 2013 ACIE paper. In particular, in their main manuscript itself,[60] this team claim that intermediate **462** would form more readily than **460**, but this position is at odds with the ΔE values that they have derived from their calculations. Now even if one assumes that these values had somehow inadvertantly got swapped around during manuscript preparation or revision, their high magnitude in either case would still make both transitions impossible to achieve in C_6H_6 at reflux, even if one interchanges them and assumes they are correct. Clearly, such a mechanism cannot possibly be operating in the hydrostannation of **440** and in our view it must therefore now be replaced with the one we have proposed in Scheme 75.

6. A Further Commentary on the Role of Catalytic Quantities Et_3B/O_2 in the Free Radical Hydrostannation of Alkyl Acetylenes with Ph_3SnH and its Role in *E/Z* Vinylstannane Isomerisation when Compared with Bu_3SnH/cat. AIBN at High Temperature

In our seminal 2005 paper on the O-directed hydrostannation of propargylically-oxygenated alkyl acetylenes with Ph_3SnH/cat. Et_3B/O_2 in PhMe at rt,[23] we reported how this new method was universally superior to the high temperature Bu_3SnH/AIBN method that had gone before it,[23] for giving α-vinylstannanes with very high levels of (*Z*)-selectivity. The very fact that we were obtaining such high selectivities clearly meant that this protocol was causing considerably less erosive (*Z*)/(*E*) vinylstannane isomerisation than its high temperature Bu_3SnH/AIBN forerunner,[3] particularly in propargylically-oxygenated alkyne systems where the α- and β-acetylenic carbons were C-branched with sizeable alkyl groups.

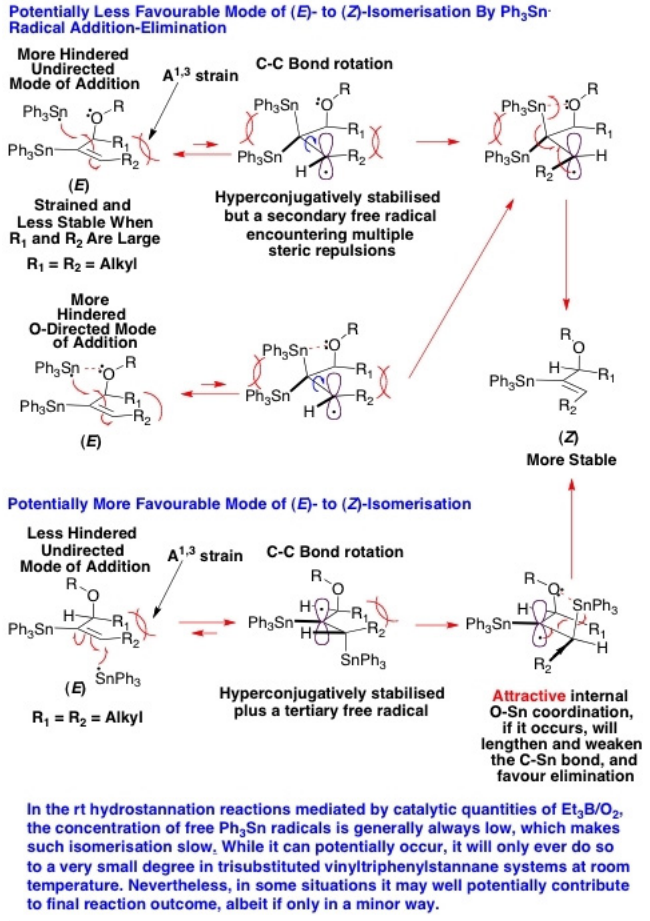
In this first paper of ours,[23] we also strongly emphasised how the O-coordinative mechanism shown in Scheme 73 was probably *the main reaction channel*[23] through which the observed (*Z*)-α-triphenylstannyl alkenes were arising with high selectivity via our new hydrostannation process, and we strongly emphasised how the minimisation of allylic $A^{1,3}$-strain and the occurrence of H-atom abstraction through the least hindered, lowest energy, transition state were most probably the primary determinants of the high (*Z*)-stereocontrol that was being observed.[23] We also emphasised how the greater Lewis acidity of Ph_3SnH and its much greater steric bulk were also likely contributing to the excellent (*Z*)-outcomes, and how operating at rt was particularly beneficial for preventing erosional equilibration of the more stable (*Z*)- to the less stable (*E*)-isomers by reversible tin radical induced addition and elimination.[23] In fact, it was only by following this general line of thinking that the reaction was first conceived by us.

Our group was also the first to invoke a possible role for Sn/vinyl radical hyperconjugative stabilisation occurring[29] in the intermediary (*Z*)-configured vinyltin radicals. However, at the time we first suggested this,[29] we specifically mentioned that no specific evidence existed for such stabilisation, and we even drew the community's attention to an article where no such stabilisation had been found for a comparable β-silyl vinyl radical.[108] Fortunately, since that time, through a set of highly insightful calculations, Alabugin et al have now provided the first good computational evidence[71] needed to support the idea that such hyperconjugative stabilisation in (*Z*)-configured vinyltin radicals is indeed substantive, and we consider it to be a major advance that these workers have now confirmed our original proposal of its very existence,[29] since such stabilisation will almost certainly lower the energy of the (*Z*)-configured transition state required to reach the favoured (*Z*)-products **436** (Scheme 73). All of these arguments that were made then, still remain valid today as to why the (Z)-vinylstannanes primarily arise from these reactions, and they are reiterated and augmented again here for *The Chemical Record.*

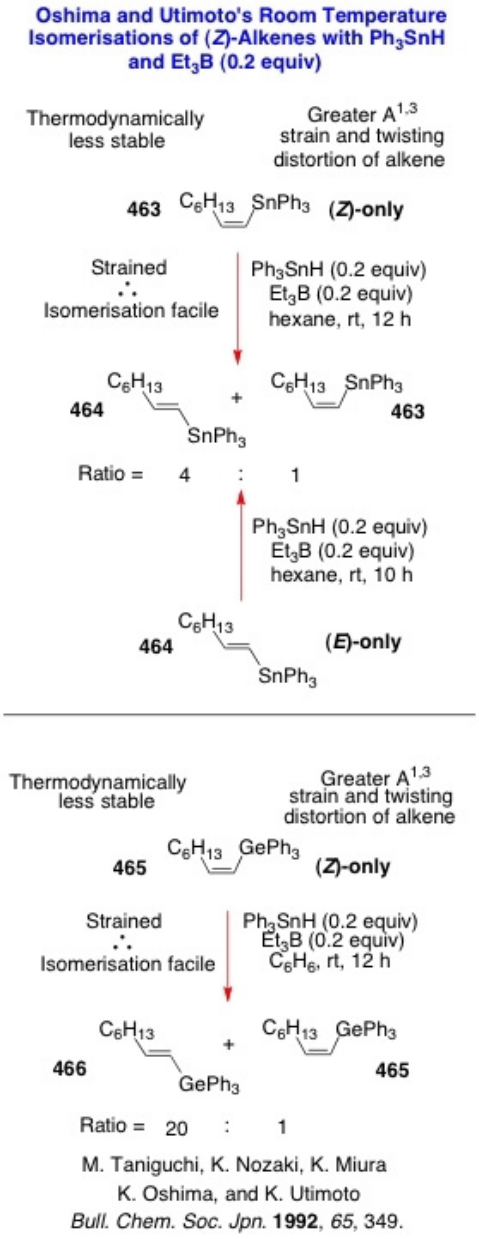
However, at the time we first wrote our three communications on this topic in 2005,[23,29,32] in one of those papers,[29] we raised the distinct possibility that Ph_3Sn radical addition-elimination might potentially be contributing to the observed stereochemical outcome, in a limited, but still possibly beneficial way, by setting up an (*E*)/(*Z*) equilibrium that could channel the small amounts of unstable (*E*)-vinyltriphenylstannanes that were potentially being formed into their more stable (*Z*)-counterparts, to relieve the significant $A^{1,3}$- and twist strain that might be present in the former isomers in some systems (Scheme 79). We had such thoughts in mind because of the prior work of Utimoto and Oshima[109] that we will shortly discuss.

We considered that in some vinyl triphenylstannane (*E*)-isomers, there might be significant torsional strain present in the alkene component, particularly if there was significant branching and/or bulky R_1 and R_2 groups, and that a reversible Ph_3Sn radical addition-elimination might potentially offer a facile way for converting these minor quantities of higher energy (*E*)-isomer into the more stable (*Z*)-vinyltriphenylstannanes over time. A similar notion had previously been advanced by Taddei and Nativi[3] in 1988 for the neat Bu_3SnH/cat. AIBN thermally mediated isomerisation reactions that they had sometimes observed. Indeed they even stated that the "larger R substituents should give an equilibrium mixture richer in *Z*- than smaller ones"[3] whenever tin radical mediated isomerisation did occur; this is perfectly reasonable.

We were led into this general direction of thought that competing *beneficial* isomerisation might potentially be occurring, to some small degree, in our rt Ph_3SnH/cat. Et_3B/O_2 alkyne hydrostannation reactions, by the aforementioned work of Utimoto and Oshima,[109] who showed that bulky, strained, (*Z*)-disubstituted vinylstannanes and alkenes will generally undergo an efficient isomerising tin radical addition-elimination reaction to the (*E*)-isomers with just the miniscule quantities of Ph_3Sn radicals that are typically being generated under the rt cat. Et_3B/O_2 radical initiating regime[85,15] (Scheme 80). However, we recognised that (*Z*)-disubstituted vinylstannane systems are very different entities structurally when compared with their trisubstituted vinyl triphenylstannane counterparts, particularly with regard to the level of steric hindrance that they provide to an incoming tin radical, which could be sufficient to make such an addition much less facile in the case of a trisubstituted



Scheme 79. Some of the possible Ph_3Sn radical mediated addition-elimination pathways that could cause isomerisation of a less stable trisubstituted (*E*)-vinyl triphenylstannane into its more stable (*Z*)-isomer, if such isomerisation proceeds at all at room temperature. Note how this process could potentially significantly relieve $A^{1,3}$ strain, if it did occur in some systems. It is entirely possible that (*E*)-systems with significant torsional strain are much more susceptible to such isomerisation. However, such a tentative proposal requires further experimental testing in such systems. Note how we include O-directed variants, which cannot be excluded given the high oxophilicity of R_3Sn groups.



Scheme 80. Utimoto and Oshima's demonstration[109] that "catalytic" amounts of Ph_3SnH/cat. Et_3B at rt can quite readily induce (Z)- to (*E*)-disubstituted alkene isomerisation by reversible Ph_3Sn radical addition-elimination. Note how the $A^{1,3}$-strained, thermodynamically less stable, (*Z*)-systems are much more susceptible to undergoing isomerisation. Possibly this is due to the (*Z*)-systems experiencing greater twisting strain in the C=C bond, which would increase their reactivity. Alternatively it might simply be a reflection of tin radical addition occurring at a similar rate to both alkenes, but the transition state for the subsequent β-elimination to the (*E*)-alkene being of lower energy than that for its (*Z*)-counterpart due to the former experiencing less steric repulsions. Note also how the degree of rt isomerisation increases in the (*E*)-isomers as the vinylic C–MR_3 bond becomes longer and further removed from the alkyl substituent.

vinylstannane, or alternatively, it could make the subsequent elimination occur much faster, if an addition did take place.

We specifically highlight these points here because this mode of initiation[85,15] usually generates only tiny amounts of Ph_3Sn radicals in solution at any one time, due to the rate of diffusion of the O_2 into the PhMe being slow, and the Et_3B autoxidation process itself being rather slow,[85] at least in its early stages, a fact that was recently verified by calculation[85h] and, before this, by experimental measurement.[85a–f] Nonetheless, Utimoto and Oshima showed[109] that the rt cat. Et_3B/O_2 radical initiating conditions were sufficient to mediate the isomerisation of a less stable (Z)-disubstituted vinylstannane (e.g. **463**) into a mixture enriched in the thermodynamically

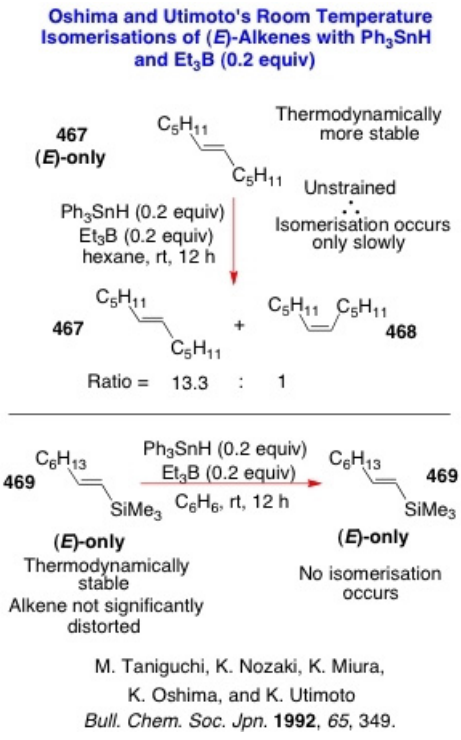
more stable (*E*)-vinylstannane (e.g. **464**) for a range of vinylstannanes (Scheme 80).[109] The position of the final (*Z*)/(*E*)-isomerising equilibrium that was ultimately established was, of course, reflective of the relative energy difference between the two geometric isomers and the activated complexes required for their formation, and the equilibrium constant K_{eq} for the reaction at room temperature.

Clearly, one could very reasonably expect the K_{eq} and the position of such equilibria to change as the temperature was raised (most especially for a reaction that was strongly heated for a very prolonged period where any significant rotameric barriers could eventually be overcome).

The results of Utimoto and Oshima[109] unambiguously demonstrated that such "catalytic" Ph_3Sn radical isomerisations could readily occur efficiently for *significantly* $A^{1,3}$*-strained*, slightly twisted, unhindered (*Z*)-1,2-disubstituted vinylstannanes at rt, even when only fairly small amounts of Ph_3Sn radicals were being generated in the reaction mixtures. Possibly these events occur more readily in the case of the (*Z*)-1,2-disubstituted systems due to them being less sterically encumbered for the initial tin radical addition. They might also be inherently much more reactive than their unstrained (*E*)-counterparts, possibly due to an increase in the HOMO energy and greater biradical character for a strained (*Z*)-1,2-disubstituted vinylstannane.

However, by the same token, the great facility of these (*Z*)- to (*E*)-isomerisations might simply be reflective of something quite different, namely: the rate of addition of Ph_3Sn radicals to the aforementioned (*E*)- and (*Z*)-disubstituted vinylstannanes and alkenes being very similar, but the ensuing β-eliminations of the resulting β-stannyl radical adducts occuring at different rates due to the different steric encumbrances that they experience; with the much faster rate of β-elimination being observed for the transition states that lead to the more stable (*E*)-isomers, due to them being of lower energy than the ones leading to the (*Z*)-vinylstannanes, which would experience far greater steric repulsions, and thus be of much higher energy. Similar arguments to these have already been advanced by Chatgilialoglu et al[110] to explain the facile *Z*/*E* isomerisation of unsaturated fatty acid esters and 2-butenes catalysed by photogenerated thiyl radicals at rt. Specifically, these workers determined that the rate constants for the addition of $HOCH_2CH_2S^{\cdot}$ to the (*Z*)- and (*E*)-forms of methyl oleate were 1.6×10^5 and $2.9\times10^5\ mol^{-1}\,sec^{-1}$ respectively while the rate constants for the corresponding β-eliminations were 1.7×10^7 and $1.6\times10^8\ sec^{-1}$, with the faster rate of elimination occurring for the transition state that led to the (*E*)-isomer, due to its activation energy being significantly lower than the one that leads to its more highly strained (*Z*)-alternative.

Utimoto and Oshima's observed outcomes[109] confirmed that for many 1,2-disubstituted alkenes the thermodynamically more stable isomers frequently do not readily isomerise to any *visibly significant* degree under the cat. $Ph_3SnH/Et_3B/O_2$ isomerisation conditions (Scheme 81).



Scheme 81. Utimoto and Oshima's demonstration[109] that "catalytic" amounts of Ph_3SnH/cat. Et_3B at rt can induce (*E*)- to (*Z*)-disubstituted alkene isomerisation by reversible Ph_3Sn radical addition-elimination. Note how the (*E*)-alkenes often isomerise less readily as the C–X bond length diminishes (X = C_5H_{11}, $SiMe_3$).

We duly took note of this data, since it suggested to us that when significantly $A^{1,3}$-strained trisubstituted vinyl triphenylstannanes of (*E*)-geometry were being formed as minor components in our initial hydrostannation reaction mixtures (i.e. structure **437** in Scheme 73), these might more readily and rapidly isomerise under such circumstances, to give the more stable (*Z*)-isomer **436**, whilst the original batch of (*Z*)-isomer **436** that was being generated might "visibly" be left unisomerised, despite it actually having undergone reversible stannyl radical addition and elimination. This would be because the radical transition state for the β-elimination back to the *trisubstituted* (*Z*)-vinylstannane **436** could potentially be significantly lower in energy and more readily attained than the corresponding transition state that would lead to formation of the (*E*)-trisubstituted vinyl triphenylstannane **437**, particularly if we were dealing with a branched $A^{1,3}$-strained system.

Basically, if the ΔG of the respective transition states for β-elimination is $>2.71\ kcal\,mol^{-1}$, this would mean that at equilibrium, more than 99% of the initial β-stannylalkyl

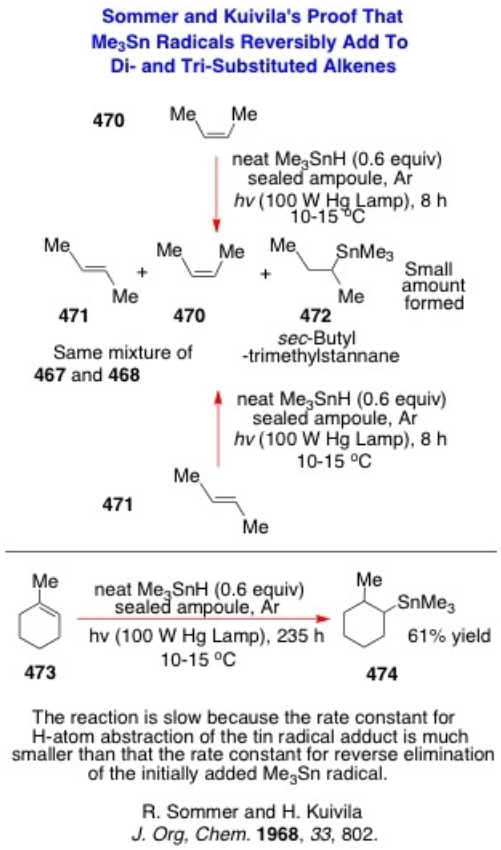
radical adducts would preferentially eliminate via the preferred lower energy (*Z*)-transition state which, in essence, would suggest that no apparent isomerisation was occurring, despite addition-elimination constantly having occurred![111]

In this regard, we draw readers' attention to Professor Neil Isaacs' very useful and insightful Table from his out-of-print textbook "*Physical Organic Chemistry*",[111] which is supplied in modified format in Table 6, and summarises how ΔG, the equilibrium constant K, and the equilibrium percentage of two chemically interconverting species A and B of differing free energy each mutually interconnect at chemical equilibrium. Significantly, it shows that just because one cannot observably see or apparently induce an isomerising interconversion of a vinylstannane to its geometric isomer at rt, this does not mean that such an equilibrium is not already in existence under the specific circumstances of the reaction, nor that stannyl radical addition-elimination is not occurring, even if only in a minor, near undetectable way, particularly when one of the isomers is 4.06 kcal mol^{-1} higher in energy.

If we return now to the issue at hand, we were also further aware of Sommer and Kuivila's work on the low temperature hydrostannation of trisubstituted alkenes under photoinitiated conditions which confirmed that Me_3Sn radicals do reversibly add to a trisubstituted alkene at temperatures as low as 10–15 °C (Scheme 82).[112]

A key point made by Sommer and Kuivila[112] in their landmark 1968 paper was that prior to their own study, it had been thought that one could not hydrostannate 1,2-disubstituted or trisubstituted alkenes under free radical conditions, due to the many repeated failures that had been encountered up until that time, when AIBN had been used to thermally initiate such reactions, although Neumann did report an alkene hydrostannation under such conditions, whilst the Kuivila work was being carried out. The multiple AIBN failures were attributed to initiator destruction by the stannanes, over the long timeframes often needed to bring about a successful alkene hydrostannation.

Given the many failures encountered in the thermally mediated AIBN chemical mode of radical initiation in alkene hydrostannation, Sommer and Kuivila eventually elected to investigate the free radical hydrostannation of *cis*-2-butene and *trans*-2-butene with Me_3SnH, in the absence of solvent, under conditions of photochemical initiation (Scheme 82).[112] Naturally, the latter conditions generate a constant and steady stream of excess tin radicals from the tin hydride or hexamethylditin, provided these reagents are present, and the photoirradiation is continuous.[72c] Most importantly, these workers observed that, after 8 h of



Scheme 82. Sommer and Kuivila's demonstration that Me_3Sn radicals add to di- and tri-substituted alkenes at low temperature.[112]

Table 6. How the equilibrium constant K and the % of the more stable molecule varies with the difference in free energy (ΔG) for two interconverting molecules A and B in equilibrium at 298 K. Clearly when there is a free energy difference of 2.71 kcal mol^{-1} between A and B, this translates to the more stable isomer predominating in the equilibrium to the tune of 99 : 1.[111]

ΔG = G(A)-G(B) = -RT ln K for A ⇌ B at 298 K

ΔG (kcal mol^{-1})	K	% of more stable molecule at equilibrium
0	1.00	50
0.24	1.50	60
0.50	2.33	70
0.82	4.00	80
1.30	9.00	90
2.71	99	99
4.06	999	99.9
5.45	9999	99.99

N. S. Isaacs in *Physical Organic Chemistry*, Chapter 2, p 86 (Longman Scientific, 1987)

irradiation at 10–15 °C, the *cis*-2-butene (*Z*)-**470** had isomerised to a mixture of *cis*- and *trans*-2-butene isomers, and that a small amount of a new substance, trimethyl-*sec*-butyltin **472** had also been formed. A similar outcome was observed when the *trans*-2-butene (*E*)-**471** was individually irradiated under identical circumstances. It was further observed when the irradiation process was conducted for 145 h, trimethyl-*sec*-butyltin **472** was now formed in 23% yield (Scheme 82), alongside tiny trace quantities of other products such as tetramethyltin or hexamethylditin, and virtually all of the unreacted Me_3SnH was recovered.

As a result of their findings, Sommer and Kuivila[112] postulated that the attack of Me_3Sn radicals upon 2-butene had to be highly reversible, and that the rate of reverse β-elimination post-addition was much faster than the key H-atom abstraction event needed to give the alkene hydrostannation product.

In light of this decisive result, Sommer and Kuivila decided to examine the photoinitiated hydrostannation of various other disubstituted alkenes, and one trisubstituted alkene, 1-methyl-cyclohexene **473**, over timeframes of between 140 and 340 h (Scheme 82).[112] In the latter case, after 235 h of irradiation at 10–15 °C under argon, a 61% yield of the hydrostannation product **474** was obtained, but it could not be ascertained whether this product had the *cis*- or *trans*-configuration relative to the β-methyl. Even so, the addition clearly took place productively at low temperature. Equally noteworthy was the fact that tetramethylethylene failed to give any *detectable* tin adduct to any significant extent under similar circumstances.

As a result of their combined studies, Sommer and Kuivila concluded[112] that stannyl radical addition was indeed occuring to di- and tri-substituted alkenes at low temperatures under the neat Me_3SnH photoinitiated conditions, but that the rate constant for the reverse elimination of the tin radical from the adduct was generally much greater than the rate constant for H-atom abstraction from the stannane by the stannyl radical adduct. Hence the very long reaction times before a notable amount of hydrostannation product could visibly be seen.

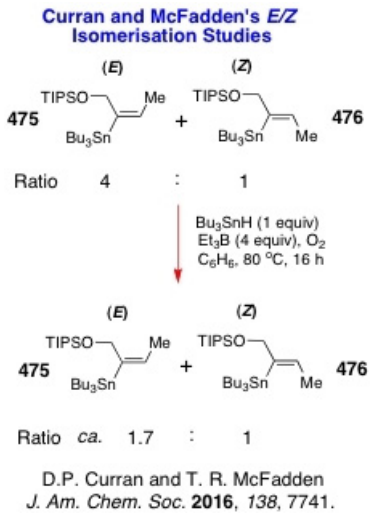
Therefore on the basis of the combined experimental evidence available back in 2005, we considered that the aforementioned Utimoto-Oshima vinyl triphenylstannane (*E*)- to (*Z*)-isomerisation pathway[109] might very well be providing a *minor* contributory reaction channel for converting *the very small quantities* of less stable, torsionally twisted, (*E*)-trisubstituted vinyl triphenylstannanes of structure **437** that might be arising (Scheme 73) into their more stable (Z)-isomers **436** via the addition-elimination pathway shown in Scheme 79, particularly if there was substantial α- and β-alkyl branching in the vinyl triphenylstannane **437**.

While we never considered this to be the primary reaction channel through which the (Z)-isomers ***436*** *would preferentially form* (see Scheme 73 for this), we did, nonetheless, accept and appreciate that such isomerisation might potentially be contributing positively towards reducing the overall amount of (*E*)-isomer **437** found at reaction end, even if not in a large or readily quantifiable way, particularly in the branched alkyl acetylene systems. We believed that such an "erosive" isomerisation would predominantly be much more successful in the conversion of a more strained branched (*E*)-trisubstituted vinyl triphenylstannane product into a less strained, lower energy, (*Z*)-isomer **436** due to this specifically relieving torsional twisting strain in the C=C double bond, and the existence of this strain often making such π-systems more reactive. We also believed that the enthalpic barrier for the reverse β-elimination of a Ph_3Sn radical from a vinylstannane β-stannyl alkyl radical adduct might be significantly lower for the transition state that would lead to the (*Z*)-vinylstannane product **436** than it would for the (*E*) particularly when there was significant $A^{1,3}$-steric repulsive strain in the (*E*)-product **437** (see Schemes 73 and 79).

Certainly, by acknowledging this possibility, we considered that we would be more closely aligning our new O-directed mechanistic proposal with the prior observations of Utimoto and Oshima on cat. Et_3B/O_2 initiated vinyl triphenylstannane isomerisation reactions with catalytic quantities of Ph_3SnH at rt, and we would be recognising that such processes could potentially be contributing to the final reaction outcome, *even if only in a minor way* under our newly defined reaction conditions.

However, quite recently, in an independent evaluation of the newly proposed β-stannylvinyl cation mechanism for alkyl acetylene hydrostannation,[60] that is quite distinct from our own, Curran and McFadden[59] examined the issue of (*E*)/(*Z*)-vinylstannane isomerisation in more detail on a quite simple trisubstituted vinylstannane system that has given powerful insights. Specifically, they subjected the (*E*)- and (*Z*)-vinylstannanes **475** and **476** to deliberate high temperature isomerisation with Bu_3SnH (1 equiv) and excess Et_3B (4 equiv) under O_2 initiated conditions at 80 °C for 16 h; a general scenario where the O_2 will have improved solubility in C_6H_6, and an enhanced ability to initiate the formation of Bu_3Sn radicals.

When they did this (Scheme 83), they did indeed induce significant trisubstituted vinylstannane isomerisation, but it was only under far more forcing (and exaggerated) high temperature conditions than we ever typically use. Their results apparently indicate that erosive (*E*)- to (*Z*)- or (*Z*)- to (*E*)-isomerisation is only a very minor contributor to geometric selectivity in relatively unhindered vinyl triphenylstannane systems under our rt Ph_3SnH conditions. However, given that this chemistry was done with the Bu_3SnH, on a



Scheme 83. Part of Curran and McFadden's study[59] on the high temperature Bu_3Sn radical mediated isomerisation of trisubstituted vinylstannanes under the Et_3B/O_2 initiation regime. Their work indicates that trisubstituted vinylstannane isomerisation via stannyl radical addition-elimination is not a major (*Z*)-stereoselectivity eroding factor in the room temperature cat. Et_3B/O_2 initiated alkyl acetylene free radical hydrostannation reactions with Bu_3SnH or Ph_3SnH, but stereochemical erosion can occur at high temperatures.

non-branched trisubstituted vinylstannane substrate that does not experience significant $A^{1,3}$-strain, it is presently difficult to extrapolate their data precisely to the action of Ph_3SnH on highly branched trisubstituted (*E*)-vinyl triphenylstannane systems, where $A^{1,3}$-strain is likely to be much more significant and of the order of 3.7–5.5 kcal mol^{-1}.[113] The latter circumstance could be envisaged to potentially produce a far more structurally perturbed and slightly twisted double bond, which ***possibly*** might give rise to enhanced double bond reactivity in some (*E*)-isomers. Clearly, further isomerisation studies are merited on such (*E*)-vinyl triphenylstannane systems with Ph_3SnH and cat. Et_3B/O_2 in PhMe at rt in order to establish whether such proposals are indeed correct but, for now, Curran and McFadden's work[59] suggests that erosive (*Z*)/(*E*)-isomerisation is minimal (or even not happening at all) in most allylically-oxygenated trisubstituted vinylstannane systems under our rt conditions, which itself only stands as a further testament to the great utility and high (*Z*)-selectivity of our O-directed free radical hydrostannation method. Organ et al have likewise found that erosive isomerisation of the product (*Z*)-trisubstituted vinyl triphenyl-stannanes is not a significant issue for the room temperature Et_3B/O_2 initiated reaction under our conditions (Scheme 25).[36]

Thus, our overall position in light of these recent mechanistic findings of Curran and McFadden,[59] is as follows. We will say that although *E/Z*-alkene isomerisation might be going on to a very small degree with trisubstituted dialkyl vinyl triphenylstannanes under our rt cat. Et_3B/O_2 initiated conditions with Ph_3SnH, the latter is not the primary reaction channel through which the (*Z*)-product **436** arises at rt. It is primarily via the O-directed stannyl radical addition and H-atom abstraction mechanism shown in Scheme 73, as we originally postulated in our very first paper on this topic in 2005.[23]

Basically, under our rt hydrostannation conditions (which, these days, we usually conduct under N_2 with a measured aliquot of air), the amount of initiating O_2 that will typically ever be present in the PhMe solution will not be that high, and when considered alongside the slow rate of S_H2 reaction that occurs between the O_2 and the Et_3B to produce the reaction-initiating Et radicals and their oxidised progeny, this will generally mean that at any fixed moment in time, the number of actual free R_3Sn radicals in the reaction mixture will thus be very small (in the absence of additional prolonged strong sunlight or UV light/photoillumination), and probably not enough to cause a visibly significant erosive isomerisation of a quite stable trisubstituted (*Z*)-vinyl triphenylstannane product **436** into its less stable (*E*)-isomer **437** via reversible stannyl radical addition-elimination. This will particularly be so, if there is significant branching in that product (*E*)-isomer, where there may be considerable rotameric hindrance and a large activation energy barrier constantly opposing attainment of the requisite radical transition state needed to bring about elimination into the (*E*)-vinylstannane **437**. Under such circumstances, it will always be difficult to observe any (*Z*)- to (*E*)-transition occurring, unless one applies sufficiently strong external heating to overcome the opposing rotameric barriers, since the initial (*Z*)-adduct will always prefer to revert back to its (*Z*)-starting material when at rt.

However, despite the number of uncomplexed tin free radicals present in the solution typically being very small under these conditions, their number might be sufficient to cause a much more facile "downhill" (*E*)- to (*Z*)-transition, particularly if an (*E*)-trisubstituted isomer **437** is considerably more strained and reactive than its (*Z*)-counterpart, and the requisite process of bond rotation to arrive at the (*Z*)-transition state is more rapid and facile, and that transition state is of much lower energy, and fully capable of readily β-eliminating into the lower energy (Z)-product. Clearly this issue of vinylstannane strain in the (*E*)/(*Z*)- and (*Z*)/(*E*)-isomerisation process via R_3Sn radical addition-elimination needs to be examined further under our room temperature conditions with Ph_3SnH/cat Et_3B with the aid suitable probe molecules aimed at bringing further mechanistic insights and understanding to the area, but for now it is clear that for most conventional systems, erosive isomerisation of the (Z)-trisubstituted vinyl triphenylstannane products by Ph_3Sn radical addition-elimination is minimal or even non-existent

under our prescribed rt conditions provided the reaction mixtures are not simultaneously exposed to strong UV light, large excesses of stannane and initiator, and high O_2 regimes for prolonged periods.

It is this greatly reduced ability to cause erosive isomerisation of the initially formed trisubstituted (*Z*)-vinylstannane products that makes our rt Ph_3SnH/cat. Et_3B hydrostannation method so useful, powerful and outstanding, particularly given the high yields of the (*Z*)-configured products **436** (Scheme 73) that it typically delivers.

The combined data gathered to date thus indicates that running these hydrostannations at room temperature, with limited quantities of Et_3B initiator, is generally the key to preventing significant observable erosive (*Z*)-trisubstituted vinyl stannane product isomerisation from occurring during the O-directed alkyl acetylene free radical hydrostannation process, and this thesis was first set out by us very clearly in 2005 when we published our first paper on this reaction,[23] and this message is again very much reiterated here.

So to summarise, Curran and McFadden's observations,[59] and the multiple papers of Organ et al before them,[36] all basically reinforce our own original assertions with respect to the Ph_3SnH/cat.Et_3B/O_2 room temperature method of O-directed alkyl acetylene free radical hydrostannation in PhMe, inasmuch as they simply confirm and reiterate that the excellent levels of *Z/E* selectivity that we typically observe are *not* generally accompanied by a significant noticably erosive (*Z*)- to (*E*)-isomerising transition; a problem that frequently plagued its poorer-performing high temperature Bu_3SnH/cat. AIBN alternative,[3] prior to our seminal work in this area in 2005. Curran and McFadden's experimental data[59] also basically support and fit the H-atom abstraction mechanism that we have proposed in Scheme 73 as the primary avenue by which the (*Z*)-trisubstituted vinyl triphenylstannanes arise and greatly predominate. However, Curran and McFadden's amended 2016 *JACS* free radical hydrostannation mechanism fails to satisfactorily explain or account for the strong regiochemical preference that is observed for the α-triphenylstannyl alkenes that are being formed in these reactions;[59] nor does the prior stannylvinyl cation mechanistic proposal that pre-dated it.[60,35a] Clearly our entirely free radical *O-directed* mechanism[23,29] of Scheme 73 does fully account for *all* of the mechanistic observations that have been made to date in this area including with respect to the observed α-regiocontrol.[29]

Like us, Curran and McFadden[59] also reject the β-stannylvinyl cation mechanistic proposal of reference [60], but largely on different grounds to ourselves and Alabugin.[71] Curran and McFadden further strongly contest[59] the additional claim by the authors of reference [37] that boric acid can serve as an effective free radical initiator in alkyne hydrostannation reactions promoted by O_2. In fact, Curran and McFadden[59] even state that boric acid has very poor solubility in C_6H_6 and PhMe, and that their control experiments showed that it played no role whatsoever in mediating the alkyne hydrostannation outcome in PhMe at 75 °C.

We too have attempted to understand this additional aspect of the reference [37] team's hydrostannation work based upon how Et_3B is known to mechanistically function as a stannyl radical initiator in the presence of O_2; a process that Davies, Ingold and Roberts[85] have suggested involves O_2 effecting the S_H2 cleavage of an Et radical from the Et_3B in the earliest stages of the initiating sequence, and the Et· subsequently abstracting hydrogen from the O-coordinated stannane, or the Et· reacting with more O_2 to give an EtOO· initiating radical which can also abstract hydrogen from the O-coordinated stannane. In fact, based on the substantial accumulated mechanistic data that has appeared in the literature until now, at least one alkyl substituent is always required on boron for such an S_H2 reaction to occur between O_2 and an alkoxyborane, which limits this mode of free radical reaction initiation to dialkoxymonoalkylboranes at best.

On top of this, and as far as we can tell, the reaction between O_2 and $B(OH)_3$ to give a hydroxyl radical has never previously been described in the literature, and the authors of reference [37] have certainly not provided any good proof that such a process does occur in their reactions, such as through spin trapping ESR spectroscopy. However, the extremely illusory way in which this team have written their paper,[37] where they have examined a series of free radical hydrostannations of a representative propargyloxy alkyl acetylene, initiated successively by O_2 and Et_3B, monoalkoxydialkyl boranes, dialkoxymonoalkyl boranes, borate esters, an alkyl boronic acid and finally $B(OH)_3$ itself, delivers a clear, if subliminally hidden, mechanistic message that all of these claimed reactions are proceeding by a common O_2-instigated S_H2 cleavage mechanism at boron, which clearly cannot be the case for boric acid and trimethylborate, which would have to lose a hydroxyl or methoxy radical respectively, by an as yet undocumented type of reaction!

Therefore, like Curran and McFadden before us,[59] we currently reject this implied mechanistic proposal by the authors of reference [37] that $B(OH)_3$ or $B(OMe)_3$ can serve as analogous free radical initiators to Et_3B/O_2, on the grounds that there is no clearly demonstrated mechanistic pathway for how they do this. We further suggest that if these latter workers are seeing any alkyne free radical hydrostannation, under these circumstances, then it is most likely due to the O_2 acting as the primary radical initiator, it generating trialkylstannyl and trialkylstannylperoxy radicals from the stannane in situ (*vide infra*), and these then going on to serve as hydrostannation initiators, as already postulated by Curran

and McFadden in their polemic[59] on the work of Organ et al.

If there is any putative possible role for boric acid in the Organ group's hydrostannation reactions, then it might be in coordinatively catalysing the homolytic breakdown of the intermediary stannyl hydroperoxides into stannyloxy and hydroxyl radicals. In this context, an obscure $B(OH)_3$-catalysed hydroperoxide homolytic cleavage process has previously been documented in the literature for alkyl hydroperoxides by Dimitrov,[114] but this does not involve the $B(OH)_3$ behaving as a genuine free radical initiator, but rather as a coordinating catalyst that facilitates homolytic fission of the O–O bond. However, even this salvitic proposal by ourselves on behalf of these workers is still unproven for stannyl hydroperoxides, and given Curran and McFadden's observations on attempted $B(OH)_3$ initiated alkyne hydrostannation, where they said that they were unable to find any significant yield differences between the hydrostannation of Organ's alkyne in PhMe (at 75 °C), either with, or without, 0.5 equiv. of $B(OH)_3$, this suggests that the latter team's experimental and mechanistic claims are in error. Therefore, on balance, we consider that this illative suggestion that $B(OH)_3$ or $B(OMe)_3$ can act in concert with O_2 to effectively initiate O-directed alkyne hydrostannations, is one that is currently unsupported.

7. Ph_3SnH Vs Bu_3SnH in Propargylically-Oxygenated Dialkyl Acetylene O-Directed Free Radical Hydrostannations. A Tale of Two Quite Different Stannanes, with Ph_3SnH Being the Far More Reactive and Superior

Finally, there are many in the community who constantly ask us why we so strongly advocate the use of Ph_3SnH/cat. Et_3B/O_2 in PhMe at rt for performing the O-directed free radical hydrostannation on complex propargylically-oxygenated dialkyl acetylene systems. The answer is quite simple: it is because Ph_3SnH and Bu_3SnH are two fundamentally different reagents in terms of their performance in this reaction, with Ph_3SnH always universally outperforming its Bu_3SnH alternative in most like-for-like substrate reaction comparisons that we have done in systems of moderate complexity, both in yield, regiocontrol and in the overall extent of starting material conversion into product. This is a point that has been explicitly made not only in our seminal 2005 paper on this reaction[23] but also in many outside research lectures that KJH has delivered since then, long before the various Organ team publications appeared, and again we reiterate this point here to encourage everyone in the community to use the Ph_3SnH/cat. Et_3B/O_2 method rather than its much poorer performing Bu_3SnH alternative which we had already evaluated and previously rejected for use in 2005.[23]

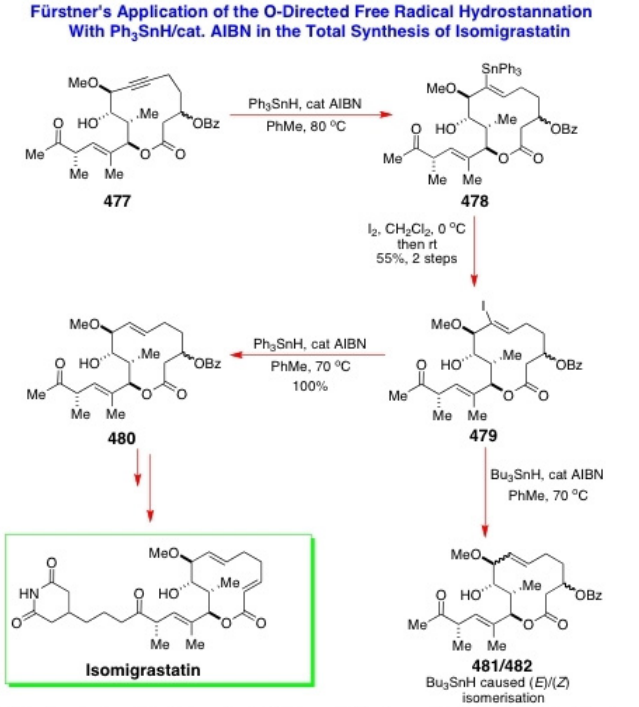
Indeed, we are exceedingly surprised by the very strong claims that have been made[36,60,37,35a] for the Bu_3SnH variant of our reaction, most especially when we ourselves[23,115] had already commented upon the generally inferior outcomes that it delivers in most alkyl acetylene systems. In fact, in our seminal paper of 2005,[23] we even went so far as to specifically argue against the use of Bu_3SnH/cat. Et_3B/O_2 by the community, following our own like-for-like reagent comparisons of Bu_3SnH/cat. Et_3B/O_2 with Ph_3SnH/cat. Et_3B/O_2 in PhMe at rt. Again, we emphasise the much poorer performance of Bu_3SnH/cat. Et_3B/O_2 here, since many in the community will unwittingly go to Bu_3SnH as their first port of call, due to this reagent being a lab staple in most laboratories, unlike its Ph_3SnH counterpart.

Because many chemists today will be totally unaware of the completely different reactivity profiles of these two reagents in the free radical hydrostannation of dialkyl acetylenes, which is a point that has consistently been made by ourselves, Utimoto and Oshima[15] (Scheme 9), Miura[16] (Scheme 9) and Konno[62] (Scheme 76), the greater majority of workers in the field will immediately turn to the Bu_3SnH/cat. Et_3B/O_2 variant of our reaction, given the reference [36] report, only to find a disappointing outcome in most systems of any real complexity, most especially with regard to yield and overall degree of starting material conversion into product, even when an excess of Bu_3SnH is used.[115] Mistakenly, they will naturally assume that the rt Ph_3SnH/cat. Et_3B/O_2 hydrostannation reaction in PhMe will perform equally badly, and many will look no further, not even bothering to try our vastly superior protocol! However, what a poorly judged decision that will have been, since usually a great synthetic dividend arises from use of rt Ph_3SnH/cat. Et_3B/O_2 in PhMe, as was found by Organ et al themselves (Scheme 25)![36]

It is precisely because of the much poorer reaction outcomes that one typically sees with Bu_3SnH/cat.Et_3B/O_2 in PhMe that we deliberately refrained from publicly endorsing and recommending this particular reagent combination for the O-directed hydrostannation of dialkyl acetylenes when we first published our work in this area back in 2005.[23] In fact, we continue to maintain this position here, notwithstanding the highly controvertive oppositional statements of reference [38]. In our opinion, the Ph_3SnH/cat.Et_3B/O_2/PhMe rt hydrostannation method remains the gold standard, and absolute pinnacle of reaction excellence in this area at present, due to it being vastly more reliable and much higher yielding than its Bu_3SnH/cat. Et_3B/O_2 counterpart in most complex synthetic theatres in which it is deployed, and it is because of this vastly superior performance that we continue to strongly endorse it here.

Indeed, there are many substrates that we have examined in our laboratory where a much worse conversion, outcome, and general overall yield has been obtained when pre-tested Bu_3SnH/cat. Et_3B/O_2 in PhMe has been used instead of Ph_3SnH/cat.Et_3B for hydrostannation, and we further note here that the Fürstner group[116] also found it necessary to utilise Ph_3SnH to bring about their O-directed free radical hydrostannation of cycloalkyne **477** in their superb isomigrastatin synthesis (Scheme 84), so emphasising the much higher reactivity and improved performance of this reagent. In fact, this particular application of the O-directed free radical hydrostannation stands out in the annals of high research excellence in the deployment of this outstanding reaction in complex molecule total synthesis, it simply being a joy to behold.

Also, the very fact that Fürstner and his team found it necessary to develop a totally new and highly efficient room temperature ruthenium-catalysed hydrostannylative method,[117,118] in order to cleanly access (*Z*)-trisubstituted vinyltributyltins of structure **484** (Scheme 85), to complete the numerous synthetic projects that were underway in their laboratory, one of which was the total synthesis of 5,6-



Scheme 84. Fürstner's application of Ph_3SnH/cat. AIBN to effect the O-directed free radical hydrostannation of cycloalkyne **477** for the total synthesis of isomigrastatin. Ph_3SnH also gave improved results to Bu_3SnH in the vinyl iodide reduction that was used to create the (*E*)-cycloalkene **480**.[116].

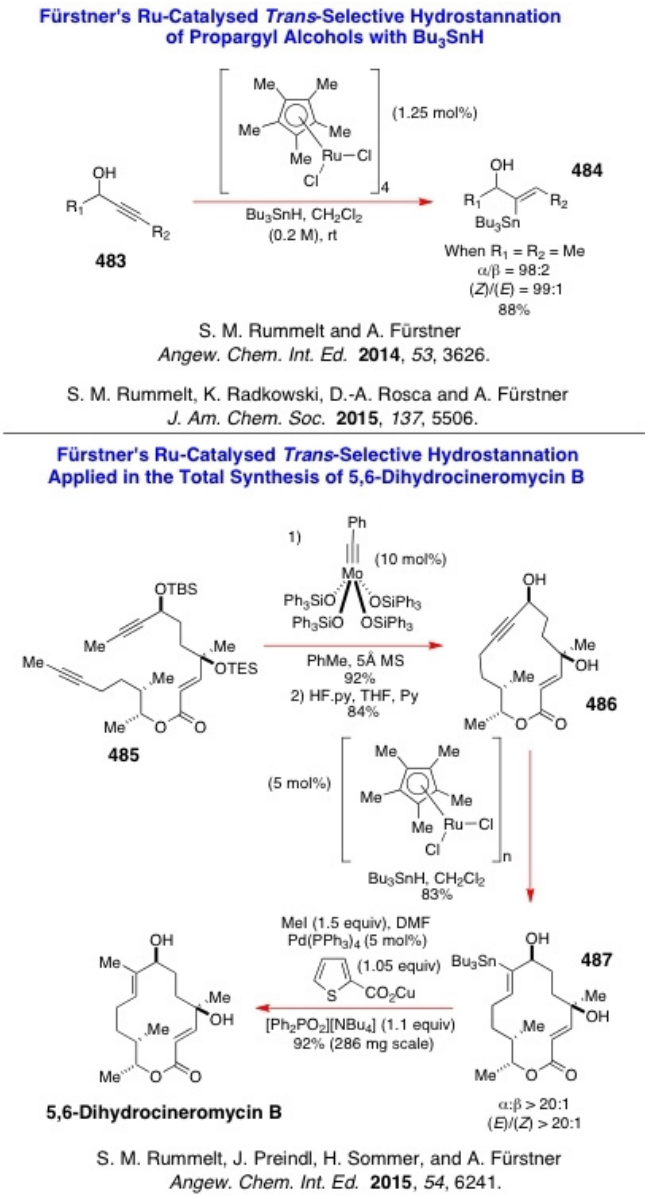
dihydrocineromycin B[119,120] (Scheme 85), speaks volumes for the poor utility of the room or higher temperature Bu_3SnH/cat. Et_3B/O_2 rt free radical hydrostannation protocol for accessing such structures. Undoubtedly, Fürstner's team would not have spent time developing their own excellent new $[Cp^*RuCl_2]_n/Bu_3SnH$ hydrostannation method for accessing such (*Z*)-configured vinyl tributylstannanes,[116,117,118] had they not perceived there to be a major methodological gap in this area, and serious deficiencies undermining the current technology available for making such vinyl tributyltins.

Likewise, had we found that Bu_3SnH worked better than Ph_3SnH under the Et_3B/O_2 room temperature initiated conditions in PhMe, when we compared the two reagents back in 2002–2005 (long before the later workers imitatively entered the area in 2012[36]), we would have recommended use of the former reagent at that time, since Bu_3SnH is much cheaper and more readily available than Ph_3SnH. However, when we published our first communication on this topic in 2005,[23] we actually argued against the use of Bu_3SnH because we had consistently found it to be a generally much poorer performing and inferior reagent in Et_3B/O_2 room temperature initiated alkyne free radical hydrostannation reactions than Ph_3SnH.[23] Also, many commercial suppliers of Bu_3SnH often supply reagent of rather dubious quality, which is not currently the case with commercial Ph_3SnH which, when newly bought, is always usually of very high quality, and the latter can be used without any noticeable deterioration if it is handled correctly inside a glovebag under N_2.

So, why is the efficacy and performance of these two reagents so remarkably different, particularly in complex disubstituted alkyne systems? We currently attribute this great difference in reactivity to the much greater H-atom donating power of Ph_3SnH towards stannylvinyl radicals compared with Bu_3SnH, which greatly favours stannyl radical addition as opposed to stannyl radical elimination in the case of the former reagent.

We also attribute this much better performance of Ph_3SnH (relative to Bu_3SnH) to the improved ability of the former O-coordinated tin radicals to accept a partnering alkyne π-electron and induce homolytic fission in a donor alkyne π-bond; a property that can be related to the relative electron affinities of the two O-coordinated Sn radicals themselves, and enhanced longevity for an O-coordinated $SnPh_3$ radical, brought about by magnified steric hindrance around the Sn atom and partial delocalisation of the radical over the three Ph rings. The latter cannot occur for an O-coordinated $SnBu_3$ radical.

With regard to the electron affinity issue, the standard electrode potential ($E^{\circ}_{R3M\ \mathbf{radical}/R3M\ anion}$) values for the conversion of $Ph_3Sn^{\cdot}$ and $Bu_3Sn^{\cdot}$ radicals into their corre-



Scheme 85. Fürstner's new Ru-catalysed *trans*-hydrostannation and Stille cross-coupling methods and their application in the total synthesis of 5,6-dihydrocineromycin B.[118,119,120]

sponding stannyl anions have been measured by voltammetry and are −0.46 V and −0.93 V respectively.[121] A more negative value for the potential means that the system has a lower electron affinity (EA) and a higher tendency to serve as an electron donor. Thus, this data reveals that a $Ph_3Sn^{\cdot}$ radical has a much greater tendency to accept an electron than does its $Bu_3Sn^{\cdot}$ counterpart. Additionally, the computed electron affinities for the $Ph_3Sn^{\cdot}$ and $Bu_3Sn^{\cdot}$ radicals are 2.08 eV (47.96 kcal mol^{-1}) and 1.52 eV (35.05 kcal mol^{-1}) respectively, as calculated using B3LYP and extended BCP basis sets. The availability of this collective data provides possible insights into the divergent chemical characters of these two radicals and potentially hints at why they react with neutral acetylenes to differing degrees. The data shows that a $Ph_3Sn^{\cdot}$ radical has a much greater ability to capture an electron from a π-radical donor such as an acetylene than does a $Bu_3Sn^{\cdot}$ radical, and undoubtedly this is due to the central Sn atom of $Ph_3Sn^{\cdot}$ being connected to the three electron-withdrawing -I phenyl groups, while its $Bu_3Sn^{\cdot}$ radical counterpart has the central Sn atom connected to three electron-donating +I Bu groups. Alongside the greatly increased H-atom donating power of Ph_3SnH towards C-centred radicals (compared with Bu_3SnH),[122] it is entirely possible that the markedly enhanced electron-accepting power of O-coordinated $Ph_3Sn^{\cdot}$ radicals might be contributing strongly to the enhanced performance of Ph_3SnH relative to Bu_3SnH in many alkyne free radical hydrostannation reactions.

It will also be appreciated that the very fact that a $Ph_3Sn^{\cdot}$ radical still has a quite large negative E^{o} value will mean that it will also retain substantial radical nucleophilicity, and one could only expect this radical nucleophilicity to further increase when the tin atom receives an extra two electrons from a donor O-atom. However, the increase in the raw positive charge on that donor O-atom could also be contributing to further enhancing the electron affinity of the tin atoms (possibly even through a Field Effect). This is the basis of the concept of **"Internal Ligand Enhanced Radicalophilicity"** that we have advanced herein, and we suggest that it is greater for O-complexed $Ph_3Sn^{\cdot}$ radicals than their O-complexed $Bu_3Sn^{\cdot}$ radical counterparts, and that this helps contribute to the greater reactivity and superior performance of the Ph_3SnH/cat. Et_3B/O_2 rt free radical hydrostannation method.

8. Summary and Final Thoughts

In this article, we have provided a thorough, critical, and broad overview of the O-directed free radical hydrostannation reaction of propargylically-oxygenated dialkyl acetylenes with Ph_3SnH/cat.Et_3B in PhMe at rt, and we have shown how this powerful new technology first came to be developed in our laboratory into one of the premier and reliable methods for stereodefined trisubstituted olefin synthesis in complex settings (the Hale-Manaviazar trisubstituted olefin synthesis).

We have also given, as best we can, an accurate historical record of the early breakthroughs in this field, most notably the key observations that were made by Corey, Ensley, Taddei, Nativi, Gielen and Willem, and Lautens. We have explained why the rt Ph_3SnH/cat.Et_3B in PhMe reaction is often so successful in this capacity, compared with its rt Bu_3SnH cat. Et_3B/O_2 or high temperature cat. AIBN counterparts, and we have countered a number of recent obtrusive mechanistic

claims that have been made by others about how our reaction proceeds.

Specifically, we have summarised the firm experimental evidence that we have gathered which supports the position that the Ph_3SnH hydrostannation reactions are genuinely O-directed and totally free radical in their nature, and all suggestions,[35a,38a,60,66] including implicit ones[59] that the regiochemistry of these processes is primarily dictated by alkyne ground state polarity have been refuted, at least for the propargylically-oxygenated alkyl acetylene systems. We have also rationalised the free radical hydrostannation outcomes of Organ[60] and Kobayashi's[61] 1-alkyl-3-trifluoromethyl propargyl alcohol systems and explained their results via a fully free radical mechanism that involves *dual* reagent O-coordination and electronic control, with both effects cooperating strongly in this specialised type of alkyne system.

In this Account, we have also collated and summarised the vast amount of hard experimental evidence that exists which independently counters and refutes the recent α-stannylvinyl cation mechanistic proposal of Organ and coworkers[60,35a,37,66] about how our O-directed free radical hydrostannation reactions proceed. Indeed, herein, we have now controverted and fully overturned all of this team's mechanistic work[60,35a,37,38] due to it misinforming the wider chemical community about a mechanism that simply does not operate for our reaction, and which could affect the community's future take up of our Ph_3SnH/cat. Et_3B rt method.

Indeed, in the present Article, we have shown that the new stannylvinyl cation mechanistic proposal of the authors of references [60] and [35] is faulty in the greater majority of the claims it has made for how these cat. Et_3B/O_2 initiated hydrostannation reactions of disubstituted acetylenes operate. Moreover, the added claim by this team[60] that the corresponding AIBN mediated hydrostannation reaction *requires* O_2 in order to proceed has not in any way been substantiated, and it is equally mechanistically unsound both from a theoretical and experimental standpoint. In fact, we would even go so far as to say that this claim is total nonsense, it demonstrating a deep misunderstanding of how AIBN mechanistically functions. In this regard, AIBN undergoes unimolecular fragmentation when thermolysed or photolysed, via a homolytic fission process that leads to the production of N_2 gas and isobutyronitrile radicals, which then go on to serve as initiating alkyl radicals for the radical chain reactions that they set in motion, including alkyne hydrostannation; this is well documented in the literature and has long been summarised in many expert texts on free radical chemistry.[122,123,124] Moreover, AIBN breaks down in exactly the same way whether it is heated in a benzene solution that contains traces of O_2 or whether the trace O_2 is missing from that solution (although in the presence of O_2 we will concede that some isobutyronitrile radicals may go on to give alkylperoxy radicals which themselves could serve as free radical reaction initiators for alkyne free radical hydrostannation). However, AIBN does not *need* O_2 to be present in order to fulfill its role and undergo this unimolecular thermal or photochemical decomposition to give the alkyne hydrostannation initiating isobutyronitrile radicals.

Indeed, the isobutyronitrile radicals that are liberated by AIBN thermolysis in *vacuum-degassed* benzene have been unambiguously characterised by ESR spectroscopy by Tabner et al at Lancaster University,[125] and their experimentally measured ESR spectrum of this radical at 333 K matches up perfectly with the calculated ESR spectrum that was obtained by computer simulation. Moreover, when a carbon centred radical such as this meets up with excess Bu_3SnH, *under oxygen free conditions*, it generally always abstracts the H-atom from the stannane to generate the Bu_3Sn radical, in a process that typically proceeds with a rate constant that lies anywhere between 0.74×10^6 to $2.0 \times 10^6\ M^{-1}s^{-1}$, according to Ingold.[126] In this respect, isobutyronitrile radicals derived from AIBN are no different from other alkyl radicals in their desire to abstract hydrogen atoms from tin hydrides *and they do not require O_2 to be present to do their job.* We thus refute this suggestion of the reference [60] authors that AIBN requires O_2 to be present in order to initiate radical reactions such as the O-directed free radical hydrostannation of acetylenes, not only because of the past ESR work that has been done by the Tabner group under O_2 free conditions,[125] but also on account of Ingold and Scaiano's rate constant determinations for Bu_3SnH by alkyl radicals,[126] which collectively demonstrate that Bu_3Sn radicals can be successfully generated by simple alkyl radicals without any need for O_2 to be present.

It is our hope that this Account has now finally brought balance, sensibility and order to an area that had suddenly become extremely confused and muddled due to these numerous incorrect mechanistic incursions by the reference [60], [35] and [37] team,[60,35,37] which have now been strongly disputed and challenged by a number of world leading groups since 2015.[59,71] This is in addition to our own very strong and robust challenge here. Indeed, notwithstanding these two earlier literature commentaries in the high-profile medium, *JACS*,[59,71] and an excellent review article on alkyne hydrometallation by Frihed and Fürstner[127] also having noted that the mechanistic proposals of the Scheme 50 team[60,35,37] are *"at odds with a previous study using substrates designed to report the presence of radical intermediates"*, this group has still continued to publicise its errant ideas through invited research seminars and papers. In this regard, they have even recently referenced their hydrostannylative mechanistic work in a December 2017 *JACS* paper.[128] This is notwithstanding Alabugin and coworkers already having

shown the impossibility of their stannylvinyl cation mechanism in 2015,[71] and ourselves having previously shown that the mechanism of alkyne hydrostannation with Ph_3SnH/cat. Et_3B had to be totally free radical back in 2005,[29] and Oshima et al before us in 1987.[15]

Hopefully, this present Account will now cause the authors of reference [60] to rethink their current untenable mechanistic position[60,35,37] for alkyne hydrostannation with the R_3SnH/cat. Et_3B system,[60,35,37] most especially now that we have advanced this much more robust and intrepid criticism of their work; a commentary that we would have preferred not to have made, but which has been required in order to refute all of their ionic mechanistic claims for dialkyl acetylene free radical hydrostannation.[60]

We hope that now with this latest, much more purposeful corrective intervention by ourselves, along with our reinstatement of the fully free radical O-directed mechanism that we first put forward for hydrostannation of propargylically-oxygenated alkyl acetylenes back in 2005 (Scheme 73),[29] that this will now finally settle matters. The same is also true for the reference [60] team's ideas concerning AIBN initiated free radical hydrostannation reactions of alkyl and aryl acetylenes,[60] which clearly do not require the co-presence of O_2 in order to proceed, and which again do not operate by way of a stannylvinyl cation.

With regard to the O-directed free radical hydrostannation of dialkyl acetylenes with Ph_3SnH and cat. Et_3B or AIBN as reaction initiators, it should now be abundantly clear to all in the field that no firm reliance can be placed upon the reference [60] claim that: "*All experiments*, *including the polar solvent studies*, *strongly suggest that cationic intermediates are involved*, *and that* O_2 *is serving as a redox catalyst in this process.*"

This statement[60] has herein been proven to be fundamentally untrue; it being based upon a series of incorrectly interpreted physical organic chemistry observations and a number of errant DFT calculations,[60] and it ignoring much past published literature in this area, including the work of our own group in reference [29] and Oshima's group in references [15a], [15b] and [15c].

We hope that this present Account by ourselves will prove useful, insightful and inspiring to future generations of chemists who will attempt to use the O-directed Ph_3SnH/cat. Et_3B free radical hydrostannation reaction in total synthesis. Certainly this has been our primary scholastic aim throughout.

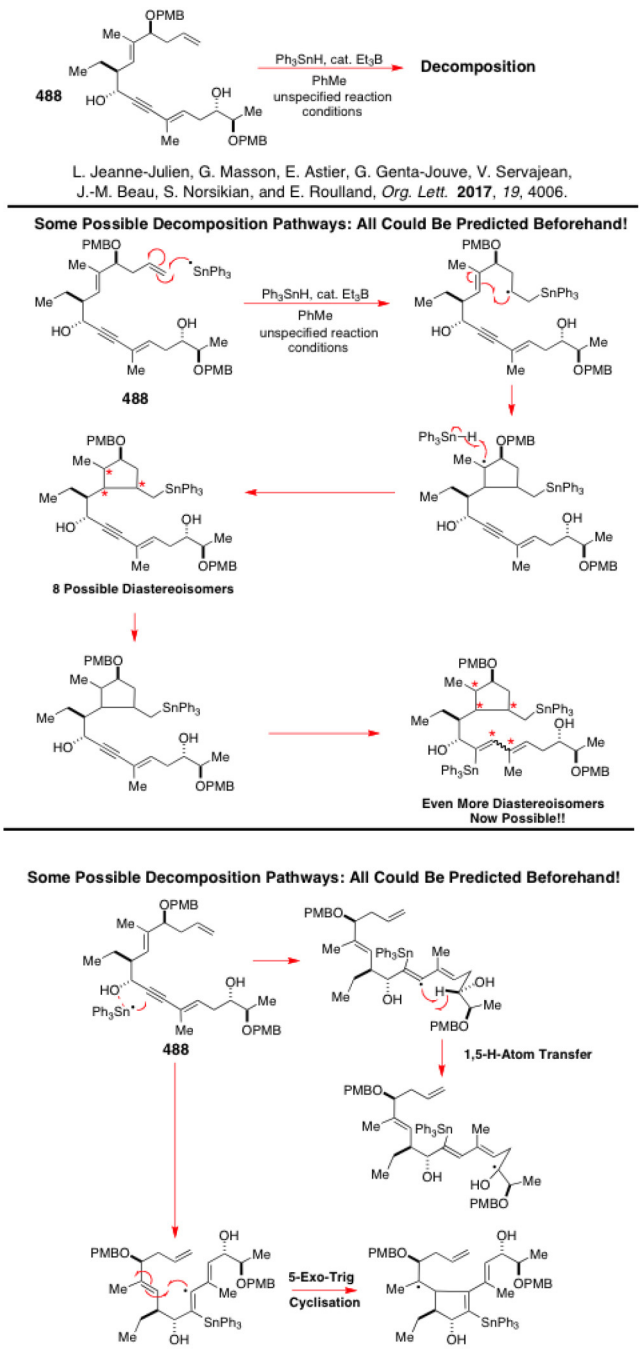
As such we strongly urge all future workers to plan their syntheses carefully, if they are proposing to use this reaction, taking special note to avoid routes or settings that could lead to injurious stannyl vinyl radical 1,5-H-atom abstraction (HA) events compromising the heteroatom stereocentres, or other features in their substrates during such hydrostannations. Clearly such events can potentially cause great problems if satisfactory countermeasures are not taken to combat them. In fact, in all of the papers that we have published to date on the use of the O-directed free radical alkyl acetylene hydrostannation in total synthesis, we have always strongly emphasised the need to examine the issue of potential stereocentre erosion via this mechanism when formulating any new synthetic plan, and we continue to highlight this issue here, since it is absolutely vital to the eventual successful use and future application of this powerful new reaction in total synthesis.

Basically, if one can see a situation arising within a substrate where either an α- or β-stannylvinyl radical has the potential to engage in such activities, then one should modify one's plan to prevent such events from ever becoming deleterious, as we did in our (+)-acutiphycin hydrostannation studies where we introduced a conformation-restraining acetal tether within the diyne substrate to overcome possible issues of this sort.

Nonetheless, and despite all of the extensive advice that we have given on this and related matters, still we see some teams attempting to incorrectly deploy our reaction on acetylenic substrates where a poor outcome could easily be predicted beforehand. One case in point is provided by the recent attempted synthesis of the tiucamycin protected macrolide using our method (Scheme 86).[129]

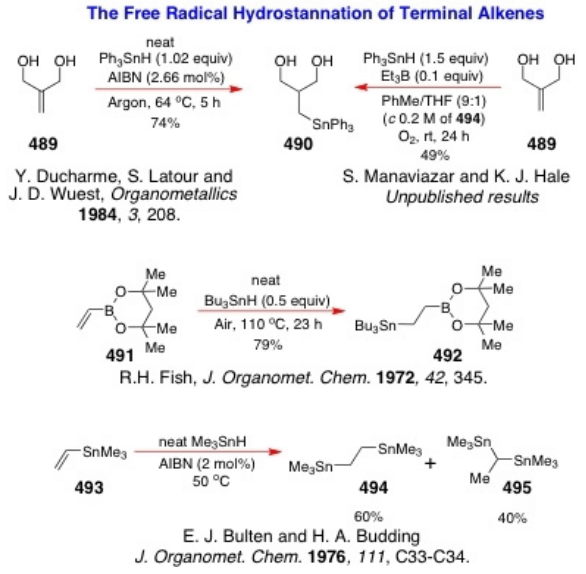
Here we see this team misapplying the O-directed free radical hydrostannation with Ph_3SnH/cat. Et_3B upon a conformationally mobile enynol system **488** that possesses a highly reactive terminal alkene unit that itself can undergo hydrostannation and/or stannyl radical addition followed by electronically favoured 5-*endo-trig* cyclisation to give a tertiary carbon radical (Scheme 86). On top of this, alkynol **488** bears an O-stereocentre that is potentially susceptible to 1,5-H-atom abstraction attended by side reactions, and there is every possibility that a 5-*exo-trig* stannyl vinyl radical cyclisation could also proceed in such a vinyl radical system, depending upon the exact reaction conditions used.

Furthermore, non-hindered enynol substrates often give rise to very poor *Z/E* stereocontrol in this process, due to their extreme sensitivity to undergoing isomerisation via stannyl radical addition/elimination under the rt Ph_3SnH/cat Et_3B hydrostannation conditions (see Scheme 26). Yet, notwithstanding all of these readily foreseeable problems, still we see this team going ahead and trying to deploy our reaction on **488**, only to encounter decomposition and a poor outcome! We have to say, here and now, that we ourselves would never have considered applying the O-directed free radical hydrostannation reaction in a system where so many competing side reactions could easily have been anticipated beforehand.



Scheme 86. The technically flawed deployment[129] of the O-directed free radical hydrostannation on the enynol **488**, which did not take into account the fact that terminal alkene units typically react with Ph_3SnH under free radical hydrostannation conditions.[130] In this case, such a competing reaction could give rise to a secondary radical that could cyclise to give a vast mix of cyclopentane structures. A range of other competing side reactions could also potentially attend such an O-directed hydrostannation process. Additionally, enynols typically give rise to *E*/*Z* mixtures when submitted to such hydrostannation processes, and we have previously commented upon this in the literature. Clearly such intermediary isomerising allyl-vinyl C-radicals can also undergo decompositional side reactions to further complicate the outcome in this instance. We ourselves would never have attempted this reaction.

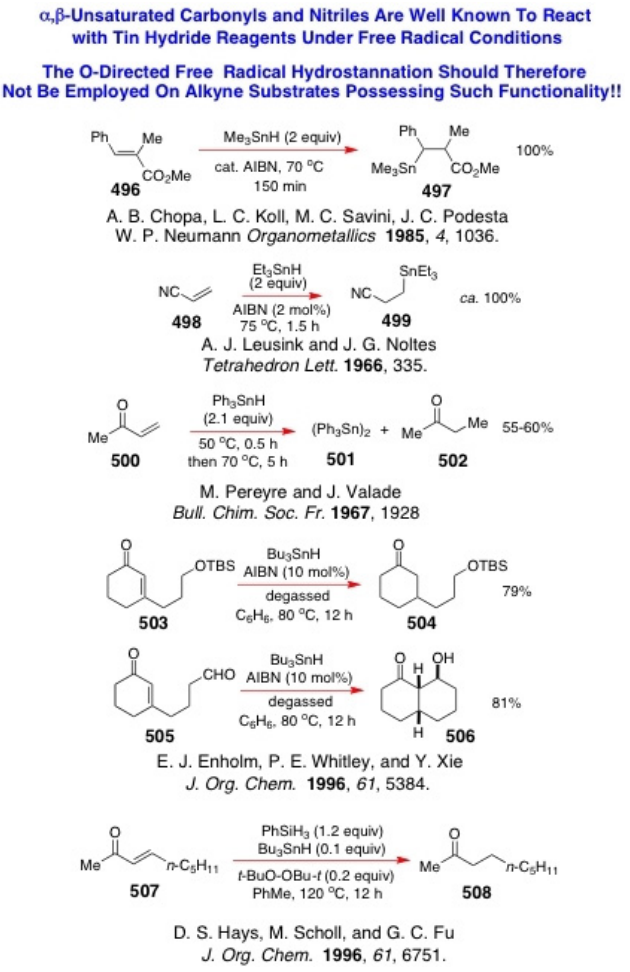
Hopefully, our discussion of these findings of reference [129] will provide readers with further guidance about how to correctly apply our method, and how one should always try to avoid implementing the process on enynols and propargylically-oxygenated alkyl acetylene systems that possess terminal alkenes (Scheme 87),[130,131,132,133] α,β-unsaturated carbonyls[134,135,136,137] and acrylonitriles (Scheme 88),[138] or other substituents that are known to react readily with tin radicals (e.g. halides, selenides, sulfides, thioacetals, xanthates, thiocarbonyls, azides,[139] phenyl ketones, nitroalkanes,[140] aldehydes,[141] vinylsulfones, etc).



Scheme 87. The free radical hydrostannation of terminal alkenes.[130,131,132]

With respect to terminal alkenes specifically, it is well known that these readily undergo free radical hydrostannation with reactive tin hydrides such as Ph_3SnH, and in this regard, we draw attention to the excellent 1984 work of Professor James D Wuest of the University of Montreal, who hydrostannated alkene **489** in 74% yield under neat AIBN thermally initiated conditions (Scheme 87).[130] We ourselves have also independently implemented this very same reaction on **489** with Ph_3SnH/cat. Et_3B in PhMe at rt (see Scheme 87) and obtained **490** in an unoptimised 49% yield, in what is an extremely clean reaction. However, there are other terminal alkenes (e.g. **491** and **493**) that will readily capture Sn radicals and go on to generate carbon centred radicals that will do a variety of things, and Scheme 87 provides two illustrative examples of such outcomes to obtain the products **492**, **494** and **495** respectively.[131,132,133]

We hope that now we have alerted readers to this reactivity profile, they will have a much greater appreciation



Scheme 88. The free radical hydrostannation of α,β-unsaturated carbonyls and nitriles is normally facile. Such functionality should be avoided in alkyne substrates that are being submitted to O-directed free radical hydrostannation.

of why such a bad outcome was obtained with the alkyne **488**; it is because the reaction was inappropriately deployed by this team.[129]

Likewise, when Fürstner et al applied our O-directed free radical hydrostannation reaction with Ph_3SnH upon the macrolide **509** (Scheme 89),[142] in their 2018 total synthesis of disciformycins A and B, it is not too surprising to find that the enone moiety that was present reacted competitively, given the very extensive past literature that now exists on how α,β-unsaturated carbonyls[133,134,135,136,137] react with stannyl radicals and stannanes (see Scheme 88). However, at least when the Fürstner team launched their reaction, they did so in full knowledge and anticipation that the enone unit would potentially undergo competing triphenylstannyl radical addition, stating that:

"As expected, attempted addition of Ph_3SnH under free radical conditions proved incompatible with the enone and led to destruction of the sensitive material".[142]

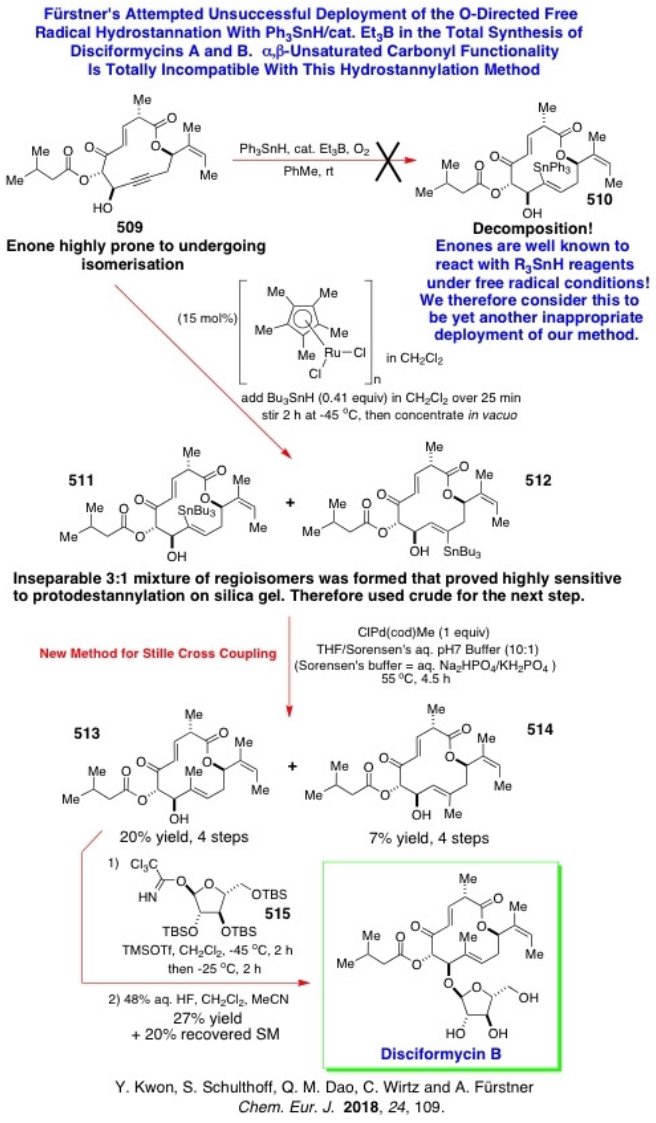
Yet again, however, and as with the **488** system,[129] we ourselves would never have considered applying this reaction in such a setting, since it is clear from the very outset that the enone unit of alkynol **509** will undergo competitive stannyl radical addition, to compromise the desired O-directed alkyne hydrostannation outcome, and this did indeed prove to be the case when this system was examined by Fürstner et al.

Indeed, it is our belief that if an alternative macrolide ring-closure strategy had been selected for this target by Fürstner et al; one that deployed the Hale-Manaviazar trisubstituted olefin synthesis much earlier on in the route, on an alkyne substrate that lacked the combined enone and 12-membered macrolide motifs, then almost certainly a much better overall result would have been obtained by this team. One that most likely would have avoided the 3:1 α:β regioisomeric mixture problem that was ultimately encountered in the formation of vinylstannanes **511** and **512**, and one that better reflected the genuine status and true synthetic worth of the Ph_3SnH hydrostannation method which, when appropriately deployed, will give extremely clean reaction outcomes in complex reaction settings, as evidenced by our well planned work on the diyne **275** in Scheme 46.

Nonetheless, with their synthesis, the Fürstner team did impressively show off the high generality and remarkable scope of their own powerful diyne RCM and Ru-catalysed O-directed hydrostannation technologies for solving complex total synthesis problems of this sort (Scheme 89), and they did this in a way that ultimately unveiled a powerful new method for vinylstannane C-methylation (one that uses stoichiometric ClPd(cod)Me) which, in itself, is highly praiseworthy and a novel new reaction tactic.

So, to summarise, enones, enoates, α,β-unsaturated amides and α,β-unsaturated nitriles are functionalities which most definitely should be absent from any starting alkyl acetylene substrate where there is a genuine desire to use the Hale-Manaviazar-Willem-Gielen Ph_3SnH/cat. Et_3B/O_2 O-directed alkyl acetylene free radical hydrostannation reaction productively and purposefully, and we hope that the community will now duly recognise and appreciate this, and deploy our method appropriately, rather than misapplying it in alkyne systems where a doomed outcome could easily be predicted before synthetic work has even begun!

While we do not claim universality of scope for our excellent alkyl acetylene hydrostannation reaction, what we do claim is an extraordinarily good likely outcome for most disubstituted alkyl acetylene systems where the reaction has been appropriately deployed with all due synthetic care and attention, and in full compliance with the detailed guidance



Scheme 89. Fürstner's new Ru-catalysed *trans*-hydrostannation method applied in the total synthesis of disciformycin B, with its new Stille cross coupling protocol for C-methylation with stoichiometric ClPd(cod)Me.[142]

and advice that has been given here. As can be seen from a thorough reading of this article, we have never shied away from exposing the limitations of our method when we or others have encountered difficulties, and we recognise that our method will not be suited to every synthetic situation that it meets. Nonetheless, there will be many future settings where we believe that our protocol will emerge as the premier method for trisubstituted olefin construction, if it is used appropriately, and this is why we have offered so much extensive advice and guidance in this Personal Account, since we wish for everyone to have a good experience and outcome when they use our chemistry, not a bad outcome! However, the obtention of a good outcome requires our fellow workers to design their syntheses carefully, as we ourselves do, and not to deploy this reaction in totally inappropriate settings where it is clear from the very outset that other reactive functionalities within the starting alkyne will thwart and compromise attainment of the desired result! The latter simply constitutes poor synthetic planning, and *no great reaction or synthetic method will ever overcome such failings in human design!*

With regard to the difficulties, we have detailed here all of the various problems that we initially faced in implementing the I–Sn exchange reaction *in highly hindered vinyl triphenylstannane systems.* While the I–Sn exchange reaction usually works very well indeed and quite rapidly with just 1.2 equiv. of either I_2 or NIS *in most non-hindered* vinyl triphenylstannane systems, *in more hindered substrates*, of the type provided by (−)-(3*R*)-inthomycin C and (+)-acutiphycin, it was ultimately found necessary to use *excess* NIS to cleave off all of the phenyl groups from the vinyltin component, before the final I–Sn exchange event could successfully be accomplished on the double bond. Also, the use of 2,6-lutidine as a base, and the highly polar MeCN as a reaction solvent, and the addition of catalytic hydroquinone as a free radical scavenger, also proved necessary to obtain high yields of the vinyl iodides from some such systems (acutiphycin), along with much longer reaction times. Nevertheless, as a result of all this hard effort and study, excellent yields have now been successfully obtained from highly hindered "recalcitrant" vinyl triphenylstannane systems of this sort using the tactics that we have described herein, devised under the auspices of the Leverhulme Trust Grant RPG-2015-438.

In this Account, we have also described the various cross-coupling protocols that have so far proven highly successful for trisubstituted alkene elaboration, and we have drawn particular attention to the great utility of the Baldwin-Lee cat. CuI/CsF variant of the Stille cross coupling reaction for trisubstituted alkene synthesis in highly hindered systems. With this important discovery Baldwin and Lee[50] have done much to advance the state of the art of cross coupling, and they have helped us to establish our O-directed hydrostannation method as one of the premier reactions presently available for complex stereodefined trisubstituted olefin synthesis with extraordinarily high stereocontrol.

Other applications of the Hale-Manaviazar trisubstituted olefin synthesis[23,32,29] in the synthetic construction of complex natural products will be reported in due course, as will additional probe studies on the O-directed free radical hydrostannation reaction mechanism[29] which will further invalidate and refute these errant stannylvinyl cation mechanistic suggestions.[60,66,35a,37]

Acknowledgements

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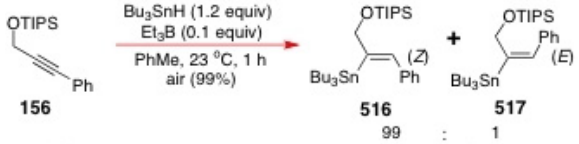
References

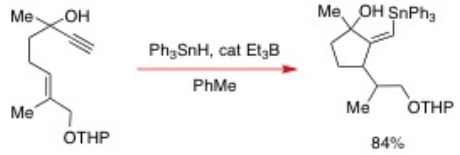
[1] E. J. Corey, R. H. Wollenberg, *J. Org. Chem.* **1975**, *40*, 2265.
[2] H. E. Ensley, R. R. Buescher, K. Lee, *J. Org. Chem.* **1982**, *47*, 404.
[3] a) C. Nativi, M. Taddei, *J. Org. Chem.* **1988**, *58*, 820; b) C. Nativi, M. Taddei, *Tetrahedron* **1989**, *45*, 1131.
[4] M. Lautens, A. H. Huboux, *Tetrahedron Lett.* **1990**, *31*, 3105.
[5] Review: B. M. Trost, Z. T. Ball, *Synthesis* **2005**, 853–877.
[6] Review: W. P. Neumann, *Synthesis*, **1987**, 665.
[7] T. Konoike, Y. Araki, *Tetrahedron Lett.* **1992**, *33*, 5093.
[8] M. J. McGrath, M. T. Fletcher, W. A. Konig, C. J. Moore, B. W. Cribb, P. G. Allsopp, W. Kitching, *J. Org. Chem.* **2003**, *68*, 3739.
[9] M. Benechie, T. Skrydstrup, F. Khuong-Huu, *Tetrahedron Lett.* **1991**, *32*, 7535.
[10] K. Miura, D. Wang, Y. Matsumoto, A. Hosomi, *Org. Lett.* **2005**, *7*, 503.
[11] K. Miura, D. Wang, Y. Matsumoto, N. Fujisawa, A. Hosomi *J. Org. Chem.* **2003**, *68*, 8730.
[12] C. M. Thiele, T. N. Mitchell, *Eur. J. Org. Chem.* **2004**, 337.
[13] M. Fujita, Y. Nakao, S. Matsunaga, M. Seiki, Y. Itoh, R. W. M. van Soest, M. Heubes, D. J. Faulkner, N. Fusetani, *Tetrahedron* **2001**, *57*, 3885.
[14] a) S. Handa, G. Pattenden, W.-S. Li, *Chem. Commun.* **1998**, 311–312; b) H. Boehm, S. Handa, G. Pattenden, L. Roberts, A. J. Blake, W.-S. Li, *J. Chem. Soc., Perkin Trans. 1* **2000**, 3522.
[15] a) K. Nozaki, K. Oshima, K. Utimoto, *J. Am. Chem. Soc.* **1987**, *109*, 2547; b) K. Nozaki, K. Oshima, K. Utimoto, *Tetrahedron* **1989**, *45*, 923; c) K. Nozaki, K. Oshima, K. Utimoto, *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3465.
[16] T. Yamakawa, H. Kinoshita, K. Miura, *J. Organomet. Chem.* **2013**, *724*, 129.
[17] H. Pan, R. Willem, J. Meunier-Piret, M. Gielen, *Organometallics* **1990**, *9*, 2199.
[18] F. Kayser, M. Biesemans, A. Delmotte, I. Verbruggen, I. De Borger, M. Gielen, R. Willem, E. Tiekink, *Organometallics* **1994**, *13*, 4026.
[19] a) D.-S. Zhu, Z.-M. Mei, C.-S. Lu, Y.-T. Zhang, W. Gao, Y. Mu, Z.-M. Wang, *J. Mol. Struct.* **2003**, *659*, 89; b) D.-S. Zhu, Z.-M. Mei, C.-S. Lu, W. Gao, Y.-T. Zhang, Y. Mu, Z.-M. Wang, *Polyhedron* **2003**, *22*, 3523; c) H. C. Dai, Q. H. Ding, X. H. Wang, S. M. Yue, H. D. Pan, X. Chen, *Polyhedron* **1998**, *17*, 2503.
[20] P. H. Dussault, C. T. Eary, R. J. Lee, U. R. Zope, *J. Chem. Soc. Perkin Trans. 1* **1999**, 2189.
[21] R. Willem, A. Delmotte, I. De Borger, M. Biesemans, M. Gielen, F. Kayser, *J. Organomet. Chem.* **1994**, *480*, 255.
[22] J. Marco-Contelles, E. Mainetti, L. Fensterbank, M. Malacria, *Eur. J Chem.* **2003**, 1759.
[23] P. Dimopoulos, A. Athlan, S. Manaviazar, J. George, M. Walters, L. Lazarides, A. E. Aliev, K. J. Hale, *Org. Lett.* **2005**, *7*, 5369.
[24] D. D. Davis, A. Surmatis, G. L. Robertson, *J. Organomet. Chem.* **1972**, *46*, C9.
[25] E. J. Corey, P. Ulrich, J. M. Fitzpatrick, *J. Am. Chem. Soc.* **1976**, *98*, 222.
[26] C. P. Jasperse, D. P. Curran, *J. Am. Chem. Soc.* **1990**, *112*, 5601.
[27] W. Kitching, H. A. Olszowy, K. Harvey, *J. Org. Chem.* **1982**, *47*, 1893.
[28] I. Rochigneux, M.-L. Fontanel, J.-C. Malanda, A. Doutheau, *Tetrahedron Lett.* **1991**, *32*, 2017.
[29] P. Dimopoulos, J. George, D. A. Tocher, S. Manaviazar, K. J. Hale, *Org. Lett.* **2005**, *7*, 5377.
[30] K. J. Hale, S. Manaviazar, J. George, *Chem. Commun.* **2011**, *46*, 4021.
[31] K. J. Hale, M. Maczka, A. Kaur, S. Manaviazar, M. Ostovar, M. Grabski, *Org. Lett.* **2014**, *16*, 1168.
[32] P. Dimopoulos, A. Athlan, S. Manaviazar, K. J. Hale, *Org. Lett.* **2005**, *7*, 5373.
[33] F. Liron, P. Le Garrec, M. Alami, *Synlett* **1999**, 246.
[34] V. I. Dodero, L. C. Koll, S. D. Mandolesi, J. C. Podesta, *J. Organometal. Chem.* **2002**, *650*, 173.
[35] a) M. S. Oderinde, R. D. J. Froese, M. G. Organ, *Chem. Eur. J.* **2014**, *20*, 8579; Although, in this article, the above team report the results of a detailed free radical hydrostannation study that they performed on aryl propargylic alcohols and their O-silyl ethers, it transpires that they did actually report their *first* free radical hydrostannation of an aryl acetylenic alcohol back in 2012,[37] when they detailed how the aryl acetylene **156** underwent regioselective hydrostannation with Bu_3SnH (1.2 equiv) in PhMe at rt in 99% yield (*Z*:*E* selectivity = 99:1),[37] using Et_3B (0.1 equiv) as the free radical initiator. See the example below (taken from reference [37]:



M. S. Oderinde, H. N. Hunter, R. D. J. Froese and M. G. Organ *Chem. Eur. J.* **2012**, *18*, 10821.

In that 2012 paper of theirs,[37] a similar incorrect statement

was made about the provenance of the O-directed free radical hydrostannation of propargylically-oxygenated aryl acetylenes, including the work done by our group in 2005[23,32] which had used Ph_3SnH/ cat. Et_3B in PhMe at rt to conduct several such O-directed hydrostannations (see Scheme 23). Significantly, as well, in that same 2014 *Chem. Eur. J.* paper of reference [35a], and as also happened in reference [60], we again see this team directly challenging[35a] our O-directed hydrostannation theory for explaining the regiochemical outcome of these free radical hydrostannations in the propargylically-oxygenated alkyl acetylene systems. Quite specifically, and in that very context, we see the following controverting statement being made by them: "*We have studied the radical mediated hydrostannylation of alkyl propargylic alcohols and their derivatives and found certain aspects of the reaction very intriguing.*[6] *For example, we reported that the regiochemical outcomes of hydrostannylation was unchanged when the hydroxy group was adorned with bulky groups, such as triisopropylsilyl (TIPS), which casts doubt on proposals that suggest tin radical (or tin hydride) coordination to the oxygen atom in the transition state controls regioselectivity.*[5] Quite clearly, the above result on **156** to obtain **516** and **517**, and the detailed mechanistic discussion and analysis (herein) of our 2005 work of reference [29] (see Scheme 47), unambiguously refutes the above statement of reference [35a]. So too does Alabugin's calculation of Scheme 54, which shows that MeO–Sn coordination in the initially formed Sn radical is actually exergonic and favourable to the tune of −2.5 kcal mol^{-1} in such hydrostannation reactions, which is quite a substantial stabilisation given the nature of the interaction and the fact that the calculation has been done for a reaction at 110 °C.[71] For the record, and whilst on this topic, in their countering statement above (which is taken directly from reference [35a]), these workers cite two papers in their accompanying reference [6]. In this *Chemical Record* article we ourselves have cited these references as: [36] and [37]. However as well as these two articles, there is a third new paper present in the reference [6] that accompanies their statement which we will now cite here as [35b]; b) M. S. Oderinde, M. G. Organ, *Angew. Chem. Int. Ed.* **2012**, *51*, 9834; We had hoped to pass this paper by without making any specific comment upon it. However, following a close inspection of it, we noticed that it duplicated and reinforced some of the same errors that had been made in reference [37], where claims were made for a trialkoxyborane serving as a free radical initiator in alkyne free radical hydrostannation reactions, when used in conjunction with molecular O_2. As we have already explained at great length in Section 6 of this Personal Account, any alkyne hydrostannation reaction that has been found to have taken place by this team under these claimed borate ester "initiating" conditions must solely be due to the $^3O_2$ acting as the radical initiator, as described in detail by Curran and McFadden in reference [59]; c) If we return now to the aforementioned statement of reference [35a], where this team directly dispute and reject the role of O–Sn coordination controlling the regiochemistry of hydrostannation in our reactions, in the reference [5] that accompanies their statement (see above), they cite the following two references of the present *Chemical Record* article, namely: reference [3a] herein by Taddei and Nativi, and reference [29] by ourselves. However, besides these two articles, they also reference two works by Oshima et al. These are references [15a] and [15b] of the present *Chemical Record* article, with the latter actually being cited incorrectly by them as a paper in *Tetrahedron Letters*, when the article had in actual fact appeared in *Tetrahedron*. Likewise, the Hale group paper that is referred to in this 2014 *Chem. Eur. J.* article[35a] (reference [29] herein) is also cited incorrectly by this team. In this aspect, the pertinent reference had one of the initials missing from the senior author's name (KJH)! While in the above two *Chemical Record* references [29] and [3a], the Hale and Taddei laboratories both argue strongly and persuasively for the idea of O-directing effects strongly controlling the observed α-regioselectivity of the free radical hydrostannation reactions of dialkyl acetylenic alcohols and ethers, this is not the case in references [15a] and [15b]. Oshima and coworkers never actually proposed that such O-coordinative control was dominating the outcomes of the terminal alkyne radical cyclisation reactions that they studied, despite the workers of reference [35a] attributing such a mechanistic proposal to them, and the latter actually observing an O-directed radical cyclisation outcome in a number of the ring-closure reactions that they had performed with Ph_3SnH/cat Et_3B. For an illustrative example of the Oshima work, where the identity of the cyclisation product yet again clearly refutes the stannylvinyl cation mechanistic proposal of references [60] and [35a], and confirms a purely free radical mechanism, see below:



K. Nozaki, K. Oshima, and K. Utimoto, *J. Am. Chem. Soc.* **1987**, *109*, 2547.

Unfortunately, when referring to the above work of Utimoto, Oshima and Nozaki[15a,15b] in their above 2014 oppositional statement to our O-directed mechanistic theory, the team of reference [35a] inaccurately represent[39] the views and work of the Oshima team, drawing them into an O–Sn coordinative control controversy, when the latter researchers never actually put forward, denied, nor endorsed such a theory.[39] So, to correct the position once and for all, there are four teams who have subscribed to the general view that the free radical hydrostannation reactions of propargylically-oxygenated dialkyl acetylenes are O-directed: the original proposers of the theory, namely, Taddei and Nativi,[3a] Willem and Geilen,[21] ourselves[23,29] and Alabugin,[71] and in the latter three cases, good solid experimental supporting evidence was gathered to back up the assertion that the O–Sn interaction dominantly controls the regiochemical outcome of such additions, including X-ray crystallography in the case of Willem and Geilen.[21] This is not the case for the authors of

references [35a] and [60] however, who, without providing any truly supportive experimental evidence, have attempted to directly call into question the entire validity of the substrate/stannane O-coordination control model.[3a,21,23,29,71] This stance was taken despite the definitive hydrostannation work that we had conducted on alkynol **293** in 2005,[29] where the regiochemistry of stannyl radical α:β-addition was found to vary quite substantially as the stannane concentration changed, which was an observation that was totally incompatible with these additions being purely electronically controlled, which would require the regiochemistry of addition never to change significantly as the stannane concentration altered, if electronic control and ground state polarity were exclusively dominating proceedings.[29]

[36] M. S. Oderinde, H. N. Hunter, M. G. Organ, *Chem. Eur. J.* **2012**, *18*, 10817.

[37] M. S. Oderinde, H. N. Hunter, R. D. J. Froese, M. G. Organ, *Chem. Eur. J.* **2012**, *18*, 10821.

[38] a) M. S. Oderinde, M. G. Organ, *Chem. Eur. J.* **2013**, *19*, 2615; b) This is the first paper where this team studied the relative rates of a free radical hydrostannation of an alkyl propargyl ether with Bu_3SnH in solvents of greatly differing polarity. Although in this paper, these workers do actually advance an exclusively free radical mechanism to explain the reaction outcomes that they observe for their hydrostannations (albeit a non-O-directed one), and this involved H-atom abstraction by a stannylvinyl radical (in line with our original 2005 proposal), this non-O-directed free radical mechanism was later rescinded by them in reference [60] and supplanted by the incorrect stannylvinyl cation mechanism shown in Scheme 50 which we are now dismantling.

[39] a) For a similar presentation of the work of others by this team in the field of Pd-catalysis, see: C. Valente, M. Pompeo, M. Sayah, M. G. Organ *Org. Process Res. Dev.* **2014**, *18*, 180; b) For an opposing response to the representation of a significant proportion of the content of reference [39a], see: D. J. Nelson, S. P. Nolan, *Org. Process Res. Dev.* **2014**, *18*, 456; c) For the reply to that contesting response, see: M. G. Organ, *Org. Process Res. Dev.* **2014**, *18*, 458.

[40] a) N.-H. Lin, L. E. Overman, M. H. Rabinowitz, L. A. Robinson, M. J. Sharp, J. Zablocki, *J. Am. Chem. Soc.* **1996**, *118*, 9062; b) L. E. Overman, K. L. Bell, F. Ito, *J. Am. Chem. Soc.* **1984**, *106*, 4192; c) L. E. Overman, R. McCready *Tetrahedron Lett.* **1982**, *23*, 4887; d) Review on pumiliotoxin alkaloid synthesis: A. Franklin, L. E. Overman, *Chem. Rev.* **1996**, *96*, 505.

[41] S. Manaviazar, K. J. Hale, A. LeFranc, *Tetrahedron Lett.* **2011**, *52*, 2080.

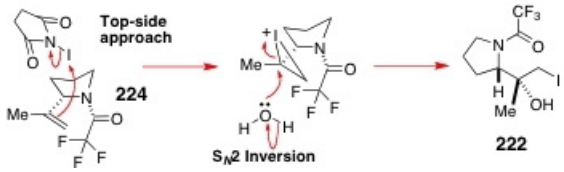
[42] G. O'Mahony, M. Nieuwenhuyzen, P. Armstrong, P. J. Stevenson, *J. Org. Chem.* **2004**, *69*, 3968.

[43] a) K. B. Sharpless, W. Amberg, Y. Bennani, G. A. Crispino, J. Hartung, K. S. Jeong, H. L. Kwong, K. Morikawa, Z. M. Wang, *J. Org. Chem.* **1992**, *57*, 2768; b) Enyne asymmetric dihydroxylation: K.-S. Jeong, P. Sjo, K. B. Sharpless, *Tetrahedron Lett.* **1992**, *33*, 3833.

[44] V. Farina, S. Kapadia, B. Krishnan, C. Wang, L. S. Liebeskind, *J. Org. Chem.* **1994**, *59*, 5909.

[45] Y. Li, K. J. Hale, *Org. Lett.* **2007**, *9*, 1267.

[46] A referee has suggested that the underside of the alkene in **224** could be sterically impeded by the N-$COCF_3$ group also, and that the NIS could attack the alkene from the top-side in the conformation shown below. They then invoke S_N2 opening by H_2O at the more electrophilic tertiary carbon of the intermediary iodonium ion giving **222**.



[47] a) Inthomycin C: T. Henkel, A. Zeeck, *Liebigs Ann. Chem.* **1991**, 367; b) For the first inthomycin ((+)-phthoxazolin/(+)-inthomycin A) to be discovered, see: S. Omura, Y. Tanaka, I. Kanaya, M. Shinose, Y. Takahashi, *J. Antibiot.* **1990**, *43*, 1034.

[48] a) K. J. Hale, M. Grabski, S. Manaviazar, M. Maczka *Org. Lett.* **2014**, *16*, 1164; b) K. J. Hale, S. Hatakeyama, F. Urabe, J. Ishihara, S. Manaviazar, M. Grabski, M. Maczka, *Org. Lett.* **2014**, *16*, 3536.

[49] B. D. Senapati, L. Gao, S. I. Lee, G.-S. Hwang, D. H. Ryu, *Org. Lett.* **2010**, *12*, 5088.

[50] S. P. H. Mee, V. Lee, J. E. Baldwin, *Angew. Chem. Int. Ed.* **2004**, *43*, 1132.

[51] D. M. Hodgson, A. M. Foley, L. T. Boulton, P. J. Lovell, G. N. Maw, *J. Chem. Soc. Perkin Trans. 1* **1999**, 2911.

[52] a) D. E. Frantz, R. Fassler, E. M. Carreira, *J. Am. Chem. Soc.* **2000**, *122*, 1806; b) D. Boyall, F. Lopez, H. Sasaki, D. E. Frantz, E. M. Carreira, *Org. Lett.* **2000**, *2*, 4233; c) D. Boyall, D. E. Frantz, E. M. Carreira, *Org. Lett.* **2002**, *4*, 2605.

[53] M. Yoshino, K. Eto, K. Takahashi, J. Ishihara, S. Hatakeyama, *Org. Biomol. Chem.* **2012**, *10*, 8164.

[54] M. R. Webb, M. S. Addie, C. M. Crawforth, J. W. Dale, X. Franci, M. Pizzonero, C. Donald, R. J. K. Taylor, *Tetrahedron* **2008**, *64*, 4778.

[55] J. J. Barchi, R. E. Moore, G. M. L. Patterson, *J. Am. Chem. Soc.* **1984**, *106*, 8193.

[56] For the total syntheses of (+)-acutiphycin that have previously been reported by the groups of Professors Amos B. Smith III, Timothy Jamison, see: a) A. B. Smith III, S. S.-Y. Chen, F. C. Nelson, J. M. Reichert, B. A. Salvatore, *J. Am. Chem. Soc.* **1995**, *117*, 12013; b) A. B. Smith, III, S. S.-Y. Chen, F. C. Nelson, J. M. Reichert, B. A. Salvatore, *J. Am. Chem. Soc.* **1997**, *119*, 10935; c) R. M. Moslin, T. F. Jamison, *J. Am. Chem. Soc.* **2006**, *128*, 15106; d) R. M. Moslin, T. F. Jamison, *J. Org. Chem.* **2007**, *72*, 9736; e) For Kiyooka's synthetic approach to (+)-acutiphycin, see: S. Kiyooka, M. A. Hena, *J. Org. Chem.* **1999**, *64*, 5511; For other approaches to various acutiphycin segments, see: f) M. S. Miftakhov, M. S. Ermolenko, I. N. Gaisina, O. M. Kuznetsov, N. K. Selezneva, Z. A. Yusupov, R. R. Muslukhov, *Russ. Chem. Bull. Int. Ed.*

2001 *50*, 1101; g) J. Methot, L. Morency, P. D. Ramsden, J. Wong, S. Leger, *Tetrahedron Lett.* **2002**, *43*, 1147.

[57] a) J. A. Marshall, N. D. Adams, *J. Org. Chem.* **1999**, *64*, 5201; b) J. A. Marshall, S. Xie, *J. Org. Chem.* **1995**, *60*, 723.

[58] a) E. A. Ilardi, C. E. Stivala, A. Zakarian, *Org. Lett.* **2008**, *10*, 1727; b) D. P. Stamos, A. G. Taylor, Y. Kishi, *Tetrahedron Lett.* **1996**, *37*, 8647; c) M. Shoji, H. Imai, M. Mukaida, K. Sakai, H. Kakeya, H. Osada, Y. Hayashi, *J. Org. Chem.* **2004**, *70*, 79.

[59] D. P. Curran, T. R. McFadden, *J. Am. Chem. Soc.* **2016**, *138*, 7741.

[60] M. S. Oderinde, R. D. J. Froese, M. G. Organ, *Angew. Chem. Int. Ed.* **2013**, *52*, 11334.

[61] Y. Hanzawa, K. Kawagoe, N. Tanahashi, Y. Kobayashi, *Tetrahedron Lett.* **1984**, *25*, 4749.

[62] J. Chae, T. Konno, M. Kanda, T. Ishihara, H. Yamanaka, *J. Fluorine Chem.* **2003**, *120*, 185.

[63] M. Newcomb in *Encyclopedia of Radicals in Chemistry, Biology and Materials*, **2012**, John Wiley & Sons: DOI:10.1002/9780470971253.rad007.

[64] B. Branchi, C. Galli, P. Gentili, *Eur. J. Org. Chem.* **2002**, 2844.

[65] L. J. Johnston, J. Lusztyk, D. D. M. Wayner, A. N. Abeywickreyma, A. L. J. Beckwith, J. C. Scaiano, K. U. Ingold, *J. Am. Chem. Soc.* **1985**, *107*, 4594.

[66] Reference 37 was the very first paper where this team suggested a role for a discrete ionic intermediate in the O-directed free radical hydrostannation reaction of propargylically-oxygenated alkyl and aryl acetylenes, in direct challenge to the work that we published in 2005 (see reference 29 and Scheme 47 herein for a summary of our work). Although a structure was never drawn by the authors of reference [37] for their illusive ionic intermediate, such structures did indeed appear in the papers that followed from this team (see references [35a] and [60] above). It was in reference [37] that these authors first commented that: *"the rate of the transformation in THF was greatly accelerated…."* compared to PhMe. For completeness of coverage, and to avoid all future doubts about the exact alkyne hydrostannation papers whose mechanistic claims we are now controverting and overturning, we will list them below, along with our reasoning and the formal reference numbers that we have given them in the main body of this *Chemical Record* article. The papers are as follows: i) M. S. Oderinde, R. D. J. Froese, M. G. Organ, *Angew. Chem. Int. Ed.* **2013**, *52*, 11334. Reference [60]. This is the paper where this team unsuccessfully attempt to marshal their claimed collective polar solvent rate acceleration data (including from reference [38a]) to support their incorrect O_2-mediated stannylvinyl cation-superoxide anion ion pair hypothesis for the free radical hydrostannation of alkyl acetylenes both under Et_3B and AIBN initiated conditions. It is also the first paper where the intermediates of the claimed ionic mechanism were actually drawn out, and where the inaccurate DFT calculations for the stannylvinyl radical to stannylvinyl cation conversions were presented, mediated by $^3O_2$; processes that are at experimental variance with how vinylic radicals react with $^3O_2$. ii) M. S. Oderinde, R. D. J. Froese, M. G. Organ, *Chem. Eur. J.* **2014**, *20*, 8579. Reference [35a]. In this paper, the above team now extend their stannylvinyl cation-superoxide anion ion pair hypothesis to the hydrostannation of propargylically-oxygenated aryl acetylene substrates. Yet again, we see the above ionic mechanism being further presented in this publication, and as previously, it is incorrect. iii) M. S. Oderinde, H. N. Hunter, R. D. J. Froese, M. G. Organ, *Chem. Eur. J.* **2012**, *18*, 10821. Reference [37]. This is the very first paper where this team suggested that a stannylvinyl cationic intermediate might possibly be arising, and where they indicate that a phenyl group will stabilize such a stannylated ionic intermediate if it was generated from a propargylically-oxygenated aryl acetylene. This is also the first paper where all of the erroneous claims were made about how $B(OH)_3/O_2$ and $B(OMe)_3/O_2$ can act as free radical initiators for alkyne hydrostannation. The boric acid initiator claim has since been challenged and criticised by Curran and McFadden in reference [59] of the present *Chemical Record* article. In Section 6 of this article, we too advance our own independent criticism of this team's $B(OH)_3/B(OMe)_3/O_2$ radical initiation claims for alkyne free radical hydrostannation which herein are simultaneously formally overturned.

[67] A. G. Harrison, F. P. Lossing, *J. Am. Chem. Soc.* **1960**, *82*, 519.

[68] F. P. Lossing, *Can. J. Chem.* **1971**, *49*, 357.

[69] J. A. Berkowitz, C. A. Mayhew, B. Ruscic, *J. Chem. Phys.* **1988**, *88*, 7396.

[70] J. A. Blush, P. Chen, *J. Phys. Chem.* **1992**, *96*, 4138.

[71] K. Pati, G. dos Passos Gomes, T. Harris, A. Hughes, H. Phan, T. Banerjee, K. Hanson, I. V. Alabugin, *J. Am. Chem. Soc.* **2015**, *137*, 1165. For Professor Alabugin's latest work in the disubstituted aryl acetylene O-directed free radical hydrostannation area, which includes further DFT calculations, see reference [143] herein.

[72] a) A. G. Davies in *Organotin Chemistry*, 2nd Edition, Wiley-VCH, Weinheim, **2004**, pp. 255; b) A. G. Davies in *Organotin Chemistry*, 2nd Edition, Wiley-VCH, Weinheim, **2004**, pp. 338; c) A. G. Davies in *Organotin Chemistry*, 2nd Edition, Wiley-VCH, Weinheim, **2004**, pp. 334; d) A. G. Davies in *Organotin Chemistry*, 2nd Edition, Wiley-VCH, Weinheim, **2004**, pp. 25.

[73] a) B. Maillard, K. U. Ingold, J. C. Scaiano *J. Am. Chem. Soc.* **1983**, *105*, 5095; b) J. C. Scaiano, *J. Am. Chem. Soc.* **1980**, *102*, 5399.

[74] J. A. Howard, J. C. Tait, S. B. Tong, *Can. J. Chem.* **1979**, *57*, 2761.

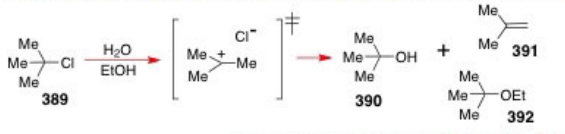
[75] R. Yang, L. Yu, X. Jin, M. Zhou, B. K. Carpenter *J. Chem. Phys.* **2005**, *122*, 014511.

[76] J.-M. Verbeek, M. Stapper, E. S. Krijnen, J.-D. van Loon, G. Lodder, S. Steenken, *J. Phys. Chem.* **1994**, *98*, 9526.

[77] a) F. O. Rice, E. Teller, *J. Chem. Phys.* **1938**, *6*, 489; b) F. O. Rice, E. Teller, *J. Chem. Phys.* **1939**, *7*, 199; c) J. Hine, *J. Am. Chem. Soc.* **1966**, *88*, 5525; d) J. Hine, *J. Org. Chem.* **1966**, *31*, 1236; e) O. S. Tee, *J. Am. Chem. Soc.* **1969**, *91*, 7144; f) O. S. Tee, K. Yates, *J. Am. Chem. Soc.* **1972**, *94*, 3074; g) J. A. Altmann, O. S. Tee, K. Yates, *J. Am. Chem. Soc.*

1976, *98*, 7132; h) For an excellent review on the Principle of Least Nuclear Motion see: J. Hine, *Adv. Phys. Org. Chem.* **1977**, *15*, 1.
[78] a) R. Mertens, C. von Sonntag, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1262; b) S. Naumov, C. von Sonntag, *J. Phys. Org. Chem.* **2005**, *18*, 586.
[79] N. Wada, K. Tokumaru, *Bull. Chem. Soc. Jpn.* **1972**, *45*, 2787.
[80] H. Mayr, N. Basso, *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1046.
[81] P. A. Byrne, S. Kobayashi, E.-U. Wurthwein, J. Ammer, H. Mayr, *J. Am. Chem. Soc.* **2017**, *139*, 1499.
[82] S. K. Pagire, P. Kreitmeier, O. Reiser, *Angew. Chem. Int. Ed. Engl.* **2017**, *56*, 10928.
[83] M. Salamone, M. Milan, G. DiLabio, M. Bietti, *J. Org. Chem.* **2013**, *78*, 5909.
[84] a) R. Mello, M. Fiorentino, C. Fusco, R. Curci, *J. Am. Chem. Soc.* **1989**, *111*, 6749; b) W. Adam, R. Curci, M. E. G. Nunez, R. Mello, *J. Am. Chem. Soc.* **1991**, *113*, 7654; c) W. W. Sander, *J. Org. Chem.* **1988**, *53*, 121.
[85] a) A. G. Davies, K. U. Ingold, B. P. Roberts, R. Tudor, *J. Chem. Soc. B*, **1971**, 698; b) A. G. Davies, B. P. Roberts, *Acc. Chem. Res.* **1972**, *5*, 387; c) A. G. Davies, *Pure Appl. Chem.* **1974**, *39*, 497; d) A. G. Davies, B. P. Roberts, in *Free Radicals*, Vol 1, J. K. Kochi (Ed.) Wiley, New York, 1973; e) P. Renaud, A. Beauseigneur, A. Brecht-Forster, B. Becattini, V. Darmency, S. Kandhasamy, F. Montermini, C. Olivier, P. Panchaud, D. Pozzi, E. M. Scanlan, A. Schaffner, V. Weber, *Pure Appl. Chem.* **2007**, *79*, 223; f) C. Olivier, P. Renaud, *Chem. Rev.* **2001**, *101*, 3415; g) C. Carra, J. C. Scaiano, *Eur. J. Org. Chem.* **2008**, 4454; h) R. Uematsu, C. Saka, Y. Sumiya, T. Ichino, T. Taketsugu, S. Maeda, *Chem. Commun.* **2017**, *53*, 7302.
[86] B. L. Williamson, P. J. Stang, A. M. Arif, *J. Am. Chem. Soc.* **1993**, *115*, 2590.
[87] For a representative example of an alkyl substituted vinyl cation eliminating to an allene, see: R. J. Hinkle, D. B. Thomas, *J. Org. Chem.* **1997**, *62*, 7534.
[88] R. Huisgen, *Pure Appl. Chem.* **1980**, *52*, 2283.
[89] R. Huisgen, *Inorg. Chem. Acta* **1980**, *40*, X2–X4.
[90] G. Steiner, R. Huisgen, *J. Am. Chem. Soc.* **1973**, *95*, 5056.
[91] H. Graf, R. Huisgen, *J. Org. Chem.* **1979**, *44*, 2594.
[92] a) K. A. Cooper, M. L. Dhar, E. D. Hughes, C. K. Ingold, B. J. McNulty, L. I. Woolf, *J. Chem. Soc.* **1948**, 2043; Clearly, in such mixed solvent S_N1 solvolysis reactions, in order to see such a large relative rate acceleration of the type observed by Hughes and Ingold (757-fold), one has to determine the reaction rate constants over a very wide range of H_2O:EtOH solvent compositions, since sampling over a very narrow compositional range will only lead to much smaller levels of relative rate acceleration being observed. Thus, as Hughes and Ingold transited from 10:90 H_2O:EtOH (i.e. 90% aqueous EtOH) up to 30:70 H_2O:EtOH (70% aqueous EtOH), their team only saw a 23.6-fold increase in the relative reaction rate. Likewise, Fainberg and Winstein only saw a 22-fold increase in relative reaction rate under identical circumstances (reference [94]). However, as soon as Ingold and Hughes raised the H_2O content of their reaction solvent to 60:40 H_2O:EtOH (i.e. 40% aqueous EtOH), it was at this point that their team did eventually see this large 757-fold rate acceleration that was finally reported. Likewise, Fainberg and Winstein ultimately observed their much greater 98,497-fold increase in relative rate acceleration only as a result of them examining this solvolysis process over an even wider aqueous EtOH compositional window. In their particular case, the ratio of H_2O:EtOH was adjusted from 2:98 (98% aqueous EtOH) to 90:10 H_2O:EtOH (10% aqueous EtOH) in order to see the massive rate acceleration that was ultimately recorded (see reference [94]). In the present instance, however, since the authors of reference [38] saw no rate acceleration at all in their O-directed free radical hydrostannation of **382** in THF + H_2O (5 equiv) (Scheme 65), but instead actually witnessed a drop in the overall reaction rate and extent of conversion into **383** (when compared to the reaction run in dry THF), this most definitely rules out any possible claim to a significant "pronounced" polar solvent rate acceleration effect operating in this reaction. This result, alongside all of the other rate data obtained by the authors of reference [38] in other polar solvents, most definitely reveals that this reaction cannot be ionic at all in its nature. Instead, the reference [38] polar solvent rate data on **382** is only compatible with an exclusively free radical mechanism for alkyne hydrostannation, of the type we have proposed, most especially when these observations are considered alongside all of the other good mechanistic evidence that we and Alabugin have both provided in references [29] and [71]. b) For Bateman, Hughes and Ingold's earlier *t*-BuCl solvolysis study of how the product proportions vary with the mol% of H_2O in the aqueous EtOH, see: L. C. Bateman, E. D. Hughes, C. K. Ingold, *J. Chem. Soc.* **1938**, 881; For a summary of their main observations, see below:

Bateman, Hughes, and Ingold's Findings of How Product Composition Varies With the % of H_2O in the EtOH in the Solvolysis of *t*-BuCl at 25 °C



		Composition of Product Mixture (Mol%)		
Vol. % H_2O in aqueous EtOH	Mols. % H_2O in aqueous EtOH	Olefin 391	Ether 392	*t*-BuOH 390
10	26.4	*ca.* 22	41	37
20	44.7	17	27	56
40	68.3	*ca.* 13	15.5	71.5

L. C. Bateman, E. D. Hughes, C. K. Ingold, *J. Chem. Soc.* **1938**, 881.

c) For an excellent overview of Sir Christopher Ingold's life, work and general contributions to the development of the Electronic Theory of Organic Chemistry, with references to reviews about Professor Ingold's life and work, see the article entitled *"Organic Pioneer"* by: J. H. Ridd, *Chemistry World*, December **2008**, 50; d) For Professor John H. Ridd's most recent historical masterpiece on Sir Christopher Ingold's work see "Christopher Ingold: The Missing Nobel Prize": J. H. Ridd in the *ACS Symposium Series, Vol. 1262, The Postumous*

Nobel Prize in Chemistry. Vol. 1. Correcting the Errors and Oversights of the Nobel Prize Committee, **2017**, Chapter 9, pp. 207; In this article, Professor Ridd (who was a highly distinguished and brilliant former coworker of Ingold) reveals how Sir Christopher Ingold was nominated for the Nobel Prize in Chemistry on 67 occasions between 1940 and 1965, including by the eminent Nobel Prize winners von-Euler Chelpin, Ruzicka, Hinshelwood and Prelog. It also discusses the people who were most likely responsible for depriving Ingold of the Prize that was rightfully his. Notwithstanding this great injustice, Ingold's memory continues to endure long after him through the impeccable, thorough, and highly trustworthy work that he did, which is continuing to help guide chemists on a true and correct course in Organic Chemistry, as we have seen herein with his Polar Solvent Rate Acceleration Theory with Hughes and its associated Rules and guidance which can be found in: e) E. D. Hughes, C. K. Ingold, *J. Chem. Soc.* **1935**, 244; and: f) E. D. Hughes, *Trans. Faraday Soc.* **1941**, *37*, 603; and: g) E. D Hughes, C. K. Ingold, *Trans. Faraday Soc.* **1941**, *37*, 657.

[93] a) E. D. Hughes, *J. Chem. Soc.* **1935**, 255; b) L. C. Bateman, K. A. Cooper, E. D. Hughes, C. K. Ingold, *J. Chem. Soc.* **1940**, 925.

[94] A. H. Fainberg, S. Winstein, *J. Am. Chem. Soc.* **1956**, *78*, 2770.

[95] N. S. Isaacs in *Physical Organic Chemistry*, Longman Scientific, **1987**, Chapter 5, pp 200-201.

[96] M. J. S. Dewar, R. S. Pyron, *J. Am. Chem. Soc.* **1970**, *92*, 3098.

[97] D. J. Cram, B. Rickborn, C. A. Kingsbury, P. Haberfield, *J. Am. Chem. Soc.* **1961**, *83*, 3678.

[98] A. Streitwieser, Y. H. Leong, *Helv. Chim. Acta*, **2012**, *95*, 1976.

[99] C. Reichardt, T. Welton, *Solvents and Solvent Effects in Organic Chemistry*, 4th Edn, **2010**, Wiley-VCH, Chapter 5, pp-165-357.

[100] M. Ochiai, Y. Takaoka, K. Sumi, Y. Nagao, *Chem. Comm.* **1986**, 1382.

[101] K. Miyamoto, M. Shiro, M. Ochiai, *Angew. Chem. Int. Ed.* **2009**, *48*, 8931.

[102] R. Gronheld, G. Lodder, T. Okuyama, *J. Org. Chem.* **2002**, 67, 693.

[103] M. Napier, C. M. Friend, *Langmuir* **1996**, *12*, 1800.

[104] X.-M. Zhang, *J. Org. Chem.* **1998**, *63*, 3590.

[105] The substantial bond strengthening effect of neighbouring CF_3 groups on attached C–H groups is discussed in detail in: a) V. Prakash Reddy in *Organofluorine Compounds in Biology and Medicine* Elsevier, **2015**, Chapter 1, General Aspects of Organofluorine Compounds, 1–27; In this Chapter, data is also presented for CF_3 groups inductively destabilising carbon-centred radicals to which they are attached. For other pertinent references that underpin these two assertions, see: b) *"Computational Study of C–H Bond Strengths in Polyfluoroalkanes"*, P. Marshall, M. Schwartz, *J. Phys. Chem. A* **1997**, *101*, 2906; c) *"BAC-MP4 Predictions of Thermochemical Data for C1 and C2 Stable Molecules and Radical Hydrofluorocarbons and Oxidized Hydrofluorocarbons"*; M. R. Zachariah, P. R. Westmoreland, D. R. F. Burgess, Jr., W. Tsang, C. F. Melius, *J. Phys. Chem.* **1996**, *100*, 8737; d) I. V. Alabugin in *Stereoelectronic Effects: A Bridge Between Structure and Reactivity*, John Wiley & Sons, **2016**, Chapter 6, pp 111.

[106] C. Tresse, S. Schweizer, P. Bisseret, J. Lalevee, G. Evano, N. Blanchard, *Synthesis* **2016**, *48*, 3317.

[107] Y. Carcenac, K. Zhine, J.-C. Kizirian, J. Thibonnet, A. Duchene, J.-L. Parrain, M. Abarbri, *Adv. Synth. Catal.* **2010**, *352*, 949.

[108] S. Lalitha, J. Chandrasekhar, *Proc. Indian Acad. Sci. Chem. Sci.* **1994**, *106*, 259–266.

[109] M. Taniguchi, K. Nozaki, K. Miura, K. Oshima, K. Utimoto, *Bull. Chem. Soc. Jpn.* **1992**, *65*, 349.

[110] a) C. Chatgilialoglu, A. Samadi, M. Guerra, H. Fischer, *ChemPhysChem* **2005**, *6*, 286; b) For related work, see: C. Chatgilialoglu, M. Ballestri, C. Ferreri, D. Vechi, *J. Org. Chem.* **1995**, *60*, 3826.

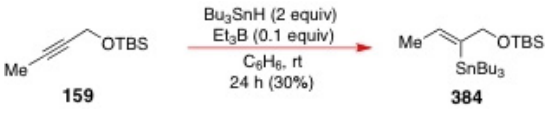
[111] N. S. Isaacs in *Physical Organic Chemistry*, Longman Scientific, **1987** Chapter 2, pp 86.

[112] R. Sommer, H. Kuivila, *J. Org. Chem.* **1968**, *33*, 802.

[113] For ab initio MO Calculated Values of Allylic 1,3-Strain see: a) L. F. Tietze, G. Schulz, *Liebigs Ann.* **1996**, 1575; b) I. V. Alabugin in *Stereoelectronic Effects: A Bridge Between Structure and Reactivity*, John Wiley & Sons, **2016**, Chapter 6, pp 116.

[114] a) D. Dimitrov, S. Voinova, N. Pencheva, *Godishnlk na Visshiya Khlm.-Tekhn. Institut, Sofiya*, 13, (No. 1,) **1966**, *133*, 175; b) For a detailed discussion of this Dimitrov work, see: W. G. Woods, R. J. Brotherton in *Prog. In Boron Chem.* **1970**, Vol 3, Ed: R. J. Brotherton, H. Steinberg, Pergamon Press, *Chapter 1*, *"Oxidations of Organic Substrates in the Presence of Boron Compounds"*, pp1–116 (this book is now available from Elsevier, 2016, via ISBN: 1483146359, 9781483146355).

[115] It has likewise been reported that the free radical hydrostannation of **159** proceeds in 30% yield with Bu_3SnH (2 equiv) and Et_3B (0.1 equiv) in C_6H_6 in the presence of O_2 at rt for 24 h. See reference [36] of this *Chemical Record* article for this example: M. S. Oderinde, H. N. Hunter, M. G. Organ, *Chem. Eur. J.* **2012**, *18*, 10817;



While in this same paper, it is also reported that the yield of (*Z*)-product **384** rises to 60% simply by stirring the reaction at rt for a prolonged period (48 h), we would say that the above 30% yield encountered by these workers is much more typical and representative of the generally inferior performance of the rt alkyne hydrostannation reactions mediated by $Bu_3SnH/Et_3B/O_2$ in PhMe, and it is the often disappointing yields of this process that are what led us to speak out so powerfully against the use of Bu_3SnH in our prior 2005 paper on this topic (see reference [23] of the present *Chemical Record* article by us). Also, others have also found that $Bu_3SnH/Et_3B/O_2$ is generally inferior and less efficient in disubstituted alkyl acetylene free radical hydrostannation

reactions, as we have stated repeatedly in our main article (see Scheme 9).
[116] K. Micoine, P. Persich, J. Llaveria, M.-H. Lam, A. Maderna, F. Lagonzo, A. Fürstner, *Chem. Eur. J.* **2013**, *19*, 7370.
[117] S. M. Rummelt, A. Fürstner, *Angew. Chem. Int. Ed.* **2014**, *53*, 3626.
[118] S. M. Rummelt, K. Radkowski, D.-A. Rosca, A. Fürstner, *J. Am. Chem. Soc.* **2015**, *137*, 5506.
[119] S. M. Rummelt, J. Preindl, H. Sommer, A. Fürstner, *Angew. Chem. Int. Ed.* **2015**, *54*, 6241.
[120] For Fürstner's optimized excellent new protocol for the direct C-methylation of vinyl tributylstannanes, see: N. Huwyler, K. Radkowski, S. M. Rummelt, A. Fürstner, *Chem. Eur. J.* **2017**, *23*, 12412.
[121] A. H. Holm, T. Brinck, K. Daasbjerg, *J. Am. Chem. Soc.* **2005**, *127*, 2677.
[122] S. Z. Zard in *Radical Reactions in Organic Synthesis* (Oxford Chemistry Masters), Oxford University Press, **2003**, Chapter 2, pp 19.
[123] D. I. Davies, M. J. Parrott in Free Radicals in Organic Synthesis (Reactivity and Structure Concepts in Organic Chemistry 7), Springer-Verlag, Berlin, **1978**, Chapter 1, pp 2.
[124] D. C. Nonhebel, J. M. Tedder, J. C. Walton in *Radicals*, Cambridge University Press, **1979**, Chapter 11, pp 113.
[125] J. C. Bevington, P. F. Fridd, B. J. Tabner, *J. Chem. Soc. Perkin Trans II*, **1982**, 1389.
[126] C. Chatgilialoglu, K. U. Ingold, J. C. Scaiano, *J. Am. Chem. Soc.* **1981**, *103*, 7739.
[127] T. G. Frihed, A. Fürstner, *Bull. Chem. Soc. Jpn.* **2016**, *89*, 135.
[128] S. Sharif, J. Day, H. N. Hunter, Y. Lu, D. Mitchell, M. J. Rodriguez, M. G. Organ, *J. Am. Chem. Soc.* **2017**, *139*, 18436.
[129] a) L. Jeanne-Julien, G. Masson, E. Astier, G. Genta-Jouve, V. Servajean, J.-M. Beau, S. Norsikian, E. Roulland, *Org. Lett.* **2017**, *19*, 4006; b) L. Jeanne-Julien, G. Masson, E. Astier, G. Genta-Jouve, V. Servajean, J.-M. Beau, S. Norsikian, E. Roulland, *J. Org. Chem.* **2018**, *83*, 921.
[130] Y. Ducharme, S. Latour, J. D. Wuest, *Organometallics* **1984**, *3*, 208.
[131] R. H. Fish, *J. Organomet. Chem.* **1972**, *42*, 345.
[132] E. J. Bulten, H. A. Budding, *J. Organomet. Chem.* **1976**, *111*, C33-C34.
[133] For other examples of tin hydrides adding to functionally substituted olefins under free radical conditions, see: R. C. Poller in *The Chemistry of Organotin Compounds, Logos Press, 1970, Chapter 7, Organotin Hydrides*, pp 105-130.
[134] A. B. Chopa, L. C. Koll, M. C. Savini, J. C. Podesta W. P. Neumann *Organometallics* **1985**, *4*, 1036.
[135] M. Pereyre, J. Valade, *Bull. Chim. Soc. Fr.* **1967**, 1928.
[136] E. J. Enholm, P. E. Whitley, Y. Xie, *J. Org. Chem.* **1996**, *61*, 5384.
[137] D. S. Hays, M. Scholl, G. C. Fu, *J. Org. Chem.* **1996**, *61*, 6751.
[138] A. J. Leusink, J. G. Noltes, *Tetrahedron Lett.* **1966**, 335.
[139] D. S. Hays, G. C. Fu, *J. Org. Chem.* **1998**, *63*, 2796.
[140] J. Tormo, D. S. Hays, G. C. Fu, *J. Org. Chem.* **1998**, *63*, 5296.
[141] D. S. Hays, G. C. Fu, *J. Am. Chem. Soc.* **1995**, *117*, 7283.
[142] Y. Kwon, S. Schulthoff, Q. M. Dao, C. Wirtz, A. Fürstner, *Chem. Eur. J.* **2018**, *24*, 109.
[143] For Professor Alabugin's latest excellent O-directed aryl acetylene free radical hydrostannation paper, where stannyl-vinyl radical cyclisation products are once more obtained, see: N. P. Tsvetkov, E. Gonzalez-Rodriguez, A. Hughes, G. dos Passos Gomes, F. D. White, F. Kuriakose, I. V. Alabugin, *Angew. Chem. Int. Ed.* **2018**, *57*, 3651.

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